

## Supplementary Table S1 and Supplementary Table S2

### Supplementary Table S1: Database-specific search strategies used for literature identification

Searches were last conducted on 20 August 2026. The expanded search strings are reproduced verbatim from the PubMed and PMC Search Details following automatic term mapping and were not manually modified. "AND" was used to combine major search concepts and "OR" to combine synonymous or related terms. Field tags included MeSH Terms, Supplementary Concept and All Fields where applicable. No language, study-design, publication-type or publication-date filters were applied at the database-search stage.

| Database | Search concept                                   | Exact search string                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Filters/limits |
|----------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| PubMed   | colorectal cancer<br>acquired<br>chemoresistance | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("acquirable"[All Fields] OR "acquire"[All Fields] OR "acquired"[All Fields] OR "acquirement"[All Fields] OR "acquirements"[All Fields] OR "acquires"[All Fields] OR "acquiring"[All Fields]) AND ("chemoresistance"[All Fields] OR "chemoresistant"[All Fields] OR "chemoresistence"[All Fields] OR "chemoresistent"[All Fields])                                                                                                                                                                                                                                                                                            | None           |
| PubMed   | colorectal cancer 5-FU<br>resistance             | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("fluorouracil"[Supplementary Concept] OR "fluorouracil"[All Fields] OR "5 fu"[All Fields] OR "fluorouracil"[MeSH Terms]) AND ("resist"[All Fields] OR "resistance"[All Fields] OR "resistances"[All Fields] OR "resistant"[All Fields] OR "resistants"[All Fields] OR "resisted"[All Fields] OR "resistence"[All Fields] OR "resistences"[All Fields] OR "resistent"[All Fields] OR "resistibility"[All Fields] OR "resisting"[All Fields] OR "resistive"[All Fields] OR "resistively"[All Fields] OR "resistivities"[All Fields] OR "resistivity"[All Fields] OR "resists"[All Fields])                                     | None           |
| PubMed   | colorectal cancer<br>oxaliplatin resistance      | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("oxaliplatin"[Supplementary Concept] OR "oxaliplatin"[All Fields] OR "oxaliplatin"[MeSH Terms] OR "oxaliplatine"[All Fields] OR "oxaliplatin s"[All Fields]) AND ("resist"[All Fields] OR "resistance"[All Fields] OR "resistances"[All Fields] OR "resistant"[All Fields] OR "resistants"[All Fields] OR "resisted"[All Fields] OR "resistence"[All Fields] OR "resistences"[All Fields] OR "resistent"[All Fields] OR "resistibility"[All Fields] OR "resisting"[All Fields] OR "resistive"[All Fields] OR "resistively"[All Fields] OR "resistivities"[All Fields] OR "resistivity"[All Fields] OR "resists"[All Fields]) | None           |

## Supplementary Table S1 and Supplementary Table S2

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|--------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| PubMed | colorectal cancer<br>irinotecan resistance               | ("colorectal neoplasms"[MeSH Terms] OR<br>("colorectal"[All Fields] AND "neoplasms"[All Fields])<br>OR "colorectal neoplasms"[All Fields] OR<br>("colorectal"[All Fields] AND "cancer"[All Fields]) OR<br>"colorectal cancer"[All Fields]) AND<br>("irinotecan"[Supplementary Concept] OR<br>"irinotecan"[All Fields] OR "irinotecan"[MeSH Terms]<br>OR "irinotecan s"[All Fields]) AND ("resist"[All Fields]<br>OR "resistance"[All Fields] OR "resistances"[All Fields]<br>OR "resistant"[All Fields] OR "resistants"[All Fields] OR<br>"resisted"[All Fields] OR "resistence"[All Fields] OR<br>"resistences"[All Fields] OR "resistent"[All Fields] OR<br>"resistibility"[All Fields] OR "resisting"[All Fields] OR<br>"resistive"[All Fields] OR "resistively"[All Fields] OR<br>"resistivities"[All Fields] OR "resistivity"[All Fields] OR<br>"resists"[All Fields]) | None |
| PubMed | colorectal cancer Wnt<br>beta-catenin<br>chemoresistance | ("colorectal neoplasms"[MeSH Terms] OR<br>("colorectal"[All Fields] AND "neoplasms"[All Fields])<br>OR "colorectal neoplasms"[All Fields] OR<br>("colorectal"[All Fields] AND "cancer"[All Fields]) OR<br>"colorectal cancer"[All Fields]) AND "Wnt"[All Fields]<br>AND ("ctnnb1 protein human"[Supplementary Concept]<br>OR "ctnnb1 protein human"[All Fields] OR "beta<br>catenin"[All Fields] OR "beta catenin"[Supplementary<br>Concept] OR "beta catenin"[MeSH Terms] OR ("beta"[All<br>Fields] AND "catenin"[All Fields])) AND<br>("chemoresistance"[All Fields] OR "chemoresistant"[All<br>Fields] OR "chemoresistence"[All Fields] OR<br>"chemoresistent"[All Fields])                                                                                                                                                                                              | None |
| PubMed | colorectal cancer<br>Notch<br>chemoresistance            | ("colorectal neoplasms"[MeSH Terms] OR<br>("colorectal"[All Fields] AND "neoplasms"[All Fields])<br>OR "colorectal neoplasms"[All Fields] OR<br>("colorectal"[All Fields] AND "cancer"[All Fields]) OR<br>"colorectal cancer"[All Fields]) AND ("notch"[All Fields]<br>OR "notch s"[All Fields] OR "notched"[All Fields] OR<br>"notches"[All Fields] OR "notching"[All Fields] OR<br>"notchings"[All Fields] OR "notchs"[All Fields]) AND<br>("chemoresistance"[All Fields] OR "chemoresistant"[All<br>Fields] OR "chemoresistence"[All Fields] OR<br>"chemoresistent"[All Fields])                                                                                                                                                                                                                                                                                         | None |
| PubMed | colorectal cancer YAP<br>chemoresistance                 | ("colorectal neoplasms"[MeSH Terms] OR<br>("colorectal"[All Fields] AND "neoplasms"[All Fields])<br>OR "colorectal neoplasms"[All Fields] OR<br>("colorectal"[All Fields] AND "cancer"[All Fields]) OR<br>"colorectal cancer"[All Fields]) AND "YAP"[All Fields]<br>AND ("chemoresistance"[All Fields] OR<br>"chemoresistant"[All Fields] OR "chemoresistence"[All<br>Fields] OR "chemoresistent"[All Fields])                                                                                                                                                                                                                                                                                                                                                                                                                                                              | None |
| PubMed | colorectal cancer stem<br>cells chemoresistance          | ("colorectal neoplasms"[MeSH Terms] OR<br>("colorectal"[All Fields] AND "neoplasms"[All Fields])<br>OR "colorectal neoplasms"[All Fields] OR<br>("colorectal"[All Fields] AND "cancer"[All Fields]) OR<br>"colorectal cancer"[All Fields]) AND ("stem cells"[MeSH<br>Terms] OR ("stem"[All Fields] AND "cells"[All Fields])<br>OR "stem cells"[All Fields]) AND ("chemoresistance"[All<br>Fields] OR "chemoresistant"[All Fields] OR                                                                                                                                                                                                                                                                                                                                                                                                                                        | None |

## Supplementary Table S1 and Supplementary Table S2

|        |                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |      |
|--------|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
|        |                                                           | "chemoresistance"[All Fields] OR "chemoresistent"[All Fields])                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |      |
| PubMed | colorectal cancer drug tolerant persister plasticity      | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND "drug"[All Fields] AND ("immune tolerance"[MeSH Terms] OR ("immune"[All Fields] AND "tolerance"[All Fields]) OR "immune tolerance"[All Fields] OR "tolerance"[All Fields] OR "drug tolerance"[MeSH Terms] OR ("drug"[All Fields] AND "tolerance"[All Fields]) OR "drug tolerance"[All Fields] OR "tolerabilities"[All Fields] OR "tolerability"[All Fields] OR "tolerable"[All Fields] OR "tolerableness"[All Fields] OR "tolerably"[All Fields] OR "tolerances"[All Fields] OR "tolerant"[All Fields] OR "tolerants"[All Fields] OR "tolerate"[All Fields] OR "tolerated"[All Fields] OR "tolerates"[All Fields] OR "tolerating"[All Fields] OR "toleration"[All Fields] OR "tolerator"[All Fields] OR "tolerators"[All Fields] OR "tolerence"[All Fields]) AND ("persist"[All Fields] OR "persistence"[All Fields] OR "persistant"[All Fields] OR "persisted"[All Fields] OR "persistence"[All Fields] OR "persistences"[All Fields] OR "persistencies"[All Fields] OR "persistency"[All Fields] OR "persistent"[All Fields] OR "persistently"[All Fields] OR "persistents"[All Fields] OR "persister"[All Fields] OR "persisters"[All Fields] OR "persisting"[All Fields] OR "persists"[All Fields]) AND ("cell plasticity"[MeSH Terms] OR "cellular plasticity"[All Fields] OR "phenotypic plasticity"[All Fields] OR "plasticity"[All Fields]) | None |
| PubMed | colorectal cancer EMT multidrug resistance                | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("epithelial-mesenchymal transition"[MeSH Terms] OR "epithelial mesenchymal transition"[All Fields] OR "EMT"[All Fields]) AND ("drug resistance, multiple"[MeSH Terms] OR ("drug"[All Fields] AND "resistance"[All Fields] AND "multiple"[All Fields]) OR "multiple drug resistance"[All Fields] OR ("multidrug"[All Fields] AND "resistance"[All Fields]) OR "multidrug resistance"[All Fields])                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | None |
| PubMed | colorectal cancer tumour microenvironment chemoresistance | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("tumour microenvironment"[All Fields] OR "tumor microenvironment"[MeSH Terms] OR ("tumor"[All Fields] AND "microenvironment"[All Fields]) OR "tumor microenvironment"[All Fields]) AND ("chemoresistance"[All Fields] OR "chemoresistant"[All Fields] OR "chemoresistence"[All Fields] OR "chemoresistent"[All Fields])                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | None |

## Supplementary Table S1 and Supplementary Table S2

|        |                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |      |
|--------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| PubMed | colorectal cancer<br>cancer associated<br>fibroblasts<br>chemoresistance     | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("cancer associated fibroblasts"[MeSH Terms] OR ("cancer associated"[All Fields] AND "fibroblasts"[All Fields]) OR "cancer associated fibroblasts"[All Fields] OR ("cancer"[All Fields] AND "associated"[All Fields] AND "fibroblasts"[All Fields]) OR "cancer associated fibroblasts"[All Fields]) AND ("chemoresistance"[All Fields] OR "chemoresistant"[All Fields] OR "chemoresistence"[All Fields] OR "chemoresistent"[All Fields])                                                                                                                                                                                                                                               | None |
| PubMed | colorectal cancer<br>immune suppression<br>chemoresistance                   | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("immunosuppression therapy"[MeSH Terms] OR ("immunosuppression"[All Fields] AND "therapy"[All Fields]) OR "immunosuppression therapy"[All Fields] OR ("immune"[All Fields] AND "suppression"[All Fields]) OR "immune suppression"[All Fields]) AND ("chemoresistance"[All Fields] OR "chemoresistant"[All Fields] OR "chemoresistence"[All Fields] OR "chemoresistent"[All Fields])                                                                                                                                                                                                                                                                                                   | None |
| PubMed | colorectal cancer<br>overcoming<br>chemoresistance<br>therapeutic strategies | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("overcome"[All Fields] OR "overcomes"[All Fields] OR "overcoming"[All Fields]) AND ("chemoresistance"[All Fields] OR "chemoresistant"[All Fields] OR "chemoresistence"[All Fields] OR "chemoresistent"[All Fields]) AND ("drug discov today ther strateg"[Journal] OR ("therapeutic"[All Fields] AND "strategies"[All Fields]) OR "therapeutic strategies"[All Fields])                                                                                                                                                                                                                                                                                                               | None |
| PMC    | colorectal cancer 5-FU<br>oxaliplatin irinotecan<br>resistance               | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("fluorouracil"[Supplementary Concept] OR "fluorouracil"[All Fields] OR "5 fu"[All Fields] OR "fluorouracil"[MeSH Terms]) AND ("oxaliplatin"[Supplementary Concept] OR "oxaliplatin"[All Fields] OR "oxaliplatin"[MeSH Terms] OR "oxaliplatine"[All Fields] OR "oxaliplatin s"[All Fields]) AND ("irinotecan"[Supplementary Concept] OR "irinotecan"[All Fields] OR "irinotecan"[MeSH Terms] OR "irinotecan s"[All Fields]) AND ("resist"[All Fields] OR "resistance"[All Fields] OR "resistances"[All Fields] OR "resistant"[All Fields] OR "resistants"[All Fields] OR "resisted"[All Fields] OR "resistence"[All Fields] OR "resistences"[All Fields] OR "resistent"[All Fields] OR | None |

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|     |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |      |
|-----|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
|     |                                                                    | "resistibility"[All Fields] OR "resisting"[All Fields] OR "resistive"[All Fields] OR "resistively"[All Fields] OR "resistivities"[All Fields] OR "resistivity"[All Fields] OR "resists"[All Fields])                                                                                                                                                                                                                                                                                                                                                                                                                                       |      |
| PMC | colorectal cancer Wnt<br>beta-catenin<br>chemoresistance           | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND "Wnt"[All Fields] AND ("ctnnb1 protein human"[Supplementary Concept] OR "ctnnb1 protein human"[All Fields] OR "beta catenin"[All Fields] OR "beta catenin"[Supplementary Concept] OR "beta catenin"[MeSH Terms] OR ("beta"[All Fields] AND "catenin"[All Fields])) AND ("chemoresistance"[All Fields] OR "chemoresistant"[All Fields] OR "chemoresistence"[All Fields] OR "chemoresistent"[All Fields]) | None |
| PMC | colorectal cancer<br>Notch YAP<br>chemoresistance                  | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("notch"[All Fields] OR "notch s"[All Fields] OR "notched"[All Fields] OR "notches"[All Fields] OR "notching"[All Fields] OR "notchings"[All Fields] OR "notchs"[All Fields]) AND "YAP"[All Fields] AND ("chemoresistance"[All Fields] OR "chemoresistant"[All Fields] OR "chemoresistence"[All Fields] OR "chemoresistent"[All Fields])                                                                | None |
| PMC | colorectal cancer<br>tumour<br>microenvironment<br>chemoresistance | ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) AND ("tumour microenvironment"[All Fields] OR "tumor microenvironment"[MeSH Terms] OR ("tumor"[All Fields] AND "microenvironment"[All Fields]) OR "tumor microenvironment"[All Fields]) AND ("chemoresistance"[All Fields] OR "chemoresistant"[All Fields] OR "chemoresistence"[All Fields] OR "chemoresistent"[All Fields])                                                                                | None |

## Supplementary Table S2. Structured evidence appraisal of all publications included in the review

**Purpose and interpretation.** This table applies the structured evidence framework described in Section 2.4 to the evidence used for mechanistic or therapeutic conclusions. Publications used only for epidemiological, clinical-treatment, pathway, methodological or other background context are retained for completeness but are marked “Not independently graded”. Evidence grades refer to the specific claim for which a publication is used in this review, not to the overall methodological quality of the publication.

**Grading criteria. Strong:** direct human/clinical validation of the specific resistance claim together with concordant mechanistic experimental evidence. **Moderate:** direct mechanistic evidence with functional validation across complementary CRC models, including organoid and/or in vivo

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evidence. **Limited:** direct evidence confined predominantly to cell-line/single-model studies, clinical association without functional causality, or incomplete functional validation. **Indirect:** evidence extrapolated from related biological, cancer or treatment contexts without direct demonstration of the specific acquired CRC chemotherapy-resistance mechanism. “Not established” is used in the main-text pathway table when no direct pathway–resistance relationship was identified; contextual sources in this supplementary table are instead marked “Not independently graded”.

| Ref. / study                | Study/source type      | Treatment or resistance context | Role in this review      | Specific claim supported                      | Direct relevance | Functional validation                     | Complementarity / human validation    | Evidence grade           | Basis for grade / key limitation                                                                                                                 |
|-----------------------------|------------------------|---------------------------------|--------------------------|-----------------------------------------------|------------------|-------------------------------------------|---------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| [1] Bray et al., 2024       | Epidemiological source | CRC epidemiology                | Contextual evidence only | Global cancer incidence and mortality context | Context only     | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [2] Rosha ndel et al., 2024 | Review/background      | CRC epidemiology                | Contextual evidence only | Epidemiology, risk factors and prevention     | Context only     | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [3] Siegel et al., 2024     | Epidemiological source | Cancer epidemiology             | Contextual evidence only | Contemporary cancer statistics                | Context only     | Not applicable for grading in             | Not independently apprais             | Not independently        | Used for clinical, biological, methodol                                                                                                          |

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|                              |                          |                       |                            |                                                                    |               |                                           |                                         |                             |                                                                                                                                                        |
|------------------------------|--------------------------|-----------------------|----------------------------|--------------------------------------------------------------------|---------------|-------------------------------------------|-----------------------------------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |                          |                       |                            |                                                                    |               | this review                               | ed for grade                            | grad ed                     | ogical or backgrou nd context; did not independ ently increase a mechanis tic or therapeut ic evidence grade.                                          |
| [4] de Gram ont et al., 2000 | Landmar k clinical trial | FOLFOX/ CRC treatment | Context ual evidenc e only | Establishe s fluoroura cil/oxalipl atin clinical treatment context | Cont ext only | Not applicable for grading in this review | Not indepen dently apprais ed for grade | Not inde pend ently grad ed | Used for clinical, biological , methodol ogical or backgrou nd context; did not independ ently increase a mechanis tic or therapeut ic evidence grade. |
| [5] Tourn igand et al., 2004 | Landmar k clinical trial | FOLFIRI/ FOLFOX       | Context ual evidenc e only | Establishe s standard treatment sequencin g                        | Cont ext only | Not applicable for grading in this review | Not indepen dently apprais ed for grade | Not inde pend ently grad ed | Used for clinical, biological , methodol ogical or backgrou nd context; did not independ ently increase a mechanis tic or therapeut ic evidence grade. |
| [6] Cassi dy et al., 2008    | Clinical trial           | CAPOX                 | Context ual evidenc e only | Establishe s capecitabi ne/oxalipl atin                            | Cont ext only | Not applicable for grading in             | Not indepen dently apprais              | Not inde pend ently         | Used for clinical, biological , methodol                                                                                                               |

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|                                    |                                   |                   |                                |                                              |                 |                                                          |                                                |                                |                                                                                                                                                                                                |
|------------------------------------|-----------------------------------|-------------------|--------------------------------|----------------------------------------------|-----------------|----------------------------------------------------------|------------------------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                                   |                   |                                | treatment<br>context                         |                 | this<br>review                                           | ed for<br>grade                                | grad<br>ed                     | ogical or<br>backgrou<br>nd<br>context;<br>did not<br>independ<br>ently<br>increase a<br>mechanis<br>tic or<br>therapeut<br>ic<br>evidence<br>grade.                                           |
| [7]<br>Morris<br>et al.,<br>2023   | Clinical<br>guideline             | Metastatic<br>CRC | Contextual<br>evidence<br>only | Current<br>systemic-<br>treatment<br>context | Context<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review | Not<br>independently<br>appraised for<br>grade | Not<br>independently<br>graded | Used for<br>clinical,<br>biological<br>,<br>methodological<br>or<br>background<br>context;<br>did not<br>independently<br>increase a<br>mechanistic<br>or<br>therapeutic<br>evidence<br>grade. |
| [8]<br>Loree<br>et al.,<br>2017    | Review                            | Metastatic<br>CRC | Contextual<br>evidence<br>only | Treatment<br>-<br>development<br>context     | Context<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review | Not<br>independently<br>appraised for<br>grade | Not<br>independently<br>graded | Used for<br>clinical,<br>biological<br>,<br>methodological<br>or<br>background<br>context;<br>did not<br>independently<br>increase a<br>mechanistic<br>or<br>therapeutic<br>evidence<br>grade. |
| [9]<br>Osterman<br>et al.,<br>2020 | Clinical/epidemiological<br>study | CRC<br>recurrence | Contextual<br>evidence<br>only | Recurrence-risk<br>context                   | Context<br>only | Not<br>applicable<br>for<br>grading in                   | Not<br>independently<br>appraised              | Not<br>independently           | Used for<br>clinical,<br>biological<br>,<br>methodol                                                                                                                                           |

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|                           |                              |                        |                          |                                                                |              | this review                               | ed for grade                          | graded                   | ological or background context; did not independently increase a mechanistic or therapeutic evidence grade.                                      |
|---------------------------|------------------------------|------------------------|--------------------------|----------------------------------------------------------------|--------------|-------------------------------------------|---------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| [10] Carlson et al., 2021 | Preclinical cell-based study | 1. Introduction        | Contextual evidence only | Used for contextual/background support in 1. Introduction.     | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [11] Blondy et al., 2020  | Review                       | 5-FU resistance        | Contextual evidence only | Background synthesis of fluoropyrimidine-resistance mechanisms | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [12] Martinez-Balibrea et | Review                       | Oxaliplatin resistance | Contextual evidence only | Background synthesis of platinum-                              | Context only | Not applicable for grading in             | Not independently appraised           | Not independently        | Used for clinical, biological, methodol                                                                                                          |

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| al., 2015                 |                                    |                 |                          | resistance mechanisms                                      |              | this review                               | ed for grade                          | graded                   | ological or background context; did not independently increase a mechanistic or therapeutic evidence grade.                                      |
| [13] Pires et al., 2010   | Preclinical cell-based study       | 1. Introduction | Contextual evidence only | Used for contextual/background support in 1. Introduction. | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [14] Gilbert et al., 2012 | Review                             | Irinotecan/TOP1 | Contextual evidence only | TOP1 biomarkers and therapeutic context                    | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [15] Wood et al., 2015    | Preclinical in vitro/in vivo study | 1. Introduction | Contextual evidence only | Used for contextual/background support                     | Context only | Not applicable for grading in             | Not independently appraised           | Not independently        | Used for clinical, biological, methodol                                                                                                          |

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|                              |                                                 |                           |                                         | in 1. Introduction.                                                        |              | this review                                                         | ed for grade                          | graded                   | logical or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [16] De Angelis et al., 2006 | Acquired 5-FU-resistant colon cancer cell lines | 5-FU resistance           | Graded mechanistic/therapeutic evidence | Stable 5-FU-resistant cells show altered treatment and recovery responses. | Yes          | Drug exposure, withdrawal and recovery/rechallenge-type assessment. | Cell-line models only.                | Limited                  | Direct acquired-resistance evidence, but validation is confined to cell models.                            |
| [17] Mola vand et al., 2025  | Review/contextual synthesis                     | CRC chemoresistance       | Contextual evidence only                | Broad drug-resistance and signalling context.                              | Context only | Not applicable for grading in this review                           | Not independently appraised for grade | Not independently graded | Used for contextual/background support only.                                                               |
| [18] Qiu et al., 2026        | Review/contextual synthesis                     | CRC chemoresistance       | Contextual evidence only                | Broad contemporary resistance - mechanism synthesis.                       | Context only | Not applicable for grading in this review                           | Not independently appraised for grade | Not independently graded | Used for contextual/background support only.                                                               |
| [19] Zhan g et al., 2008     | Review                                          | 5-FU mechanism/resistance | Contextual evidence only                | Pharmacological and molecular background for 5-FU resistance.              | Context only | Not applicable for grading in this review                           | Not independently appraised for grade | Not independently graded | Used for background synthesis only.                                                                        |
| [20] Peters et al., 2002     | Review                                          | 5-FU/TYMS                 | Contextual evidence only                | TYMS and fluoropyrimidine-response context.                                | Context only | Not applicable for grading in this review                           | Not independently appraised for grade | Not independently graded | Used for clinical/mechanistic context rather than independent grading.                                     |

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|                                                |                                                               |                                                                    |                                                           |                                                                                                                                                                                                                                               |                              |                                                                                                                                      |                                                                                                                                                                                        |                                         |                                                                                                                                                                                                                                                                                                         |
|------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [21]<br>Verm<br>a et<br>al.,<br>2022           | Review                                                        | 5-<br>FU/DPD                                                       | Context<br>ual<br>evidenc<br>e only                       | DPD-<br>mediated<br>fluoropyri<br>midine<br>metabolis<br>m/resista<br>nce<br>context.                                                                                                                                                         | Cont<br>ext<br>only          | Not<br>applicable<br>for<br>grading in<br>this<br>review                                                                             | Not indepen<br>dently<br>apprais<br>ed for<br>grade                                                                                                                                    | Not inde<br>pend<br>ently<br>grad<br>ed | Secondar<br>y<br>evidence<br>only.                                                                                                                                                                                                                                                                      |
| [22]<br>Gmei<br>ner et<br>al.,<br>2023         | Review/c<br>ontextual<br>synthesis                            | 5-FU<br>metabolis<br>m                                             | Context<br>ual<br>evidenc<br>e only                       | Fluoropyr<br>imidine<br>pharmacol<br>ogy and<br>resistance<br>context.                                                                                                                                                                        | Cont<br>ext<br>only          | Not<br>applicable<br>for<br>grading in<br>this<br>review                                                                             | Not indepen<br>dently<br>apprais<br>ed for<br>grade                                                                                                                                    | Not inde<br>pend<br>ently<br>grad<br>ed | Secondar<br>y<br>contextua<br>l source<br>only.                                                                                                                                                                                                                                                         |
| [23]<br>Zhan<br>g et<br>al.,<br>2020           | CRC cell,<br>mouse<br>and<br>human<br>translatio<br>nal study | 5-FU<br>resistance<br>; DPD-<br>mediated<br>drug<br>catabolis<br>m | Graded<br>mechani<br>stic/ther<br>apeutic<br>evidenc<br>e | SphK2<br>promotes<br>H3K56ac-<br>mediated<br>DPD<br>expressio<br>n and 5-<br>FU<br>catabolis<br>m,<br>thereby<br>conferrin<br>g 5-FU<br>resistance;<br>SphK2<br>inhibition<br>reverses<br>resistance<br>in<br>experime<br>ntal CRC<br>models. | Yes                          | SphK2<br>genetic/ph<br>armacolog<br>ical<br>manipulati<br>on, ChIP-<br>seq/lucifer<br>ase assays<br>and 5-FU<br>response<br>testing. | CRC<br>cell<br>lines,<br>transge<br>nic/kno<br>ckout<br>and<br>xenogra<br>ft<br>mouse<br>models,<br>plus<br>human<br>CRC<br>tissue<br>showin<br>g<br>SphK2-<br>DPD<br>associat<br>ion. | Mod<br>erate                            | Direct<br>functiona<br>l<br>resistance<br>mechanis<br>m<br>validated<br>across<br>complem<br>entary in<br>vitro and<br>in vivo<br>CRC<br>models;<br>human<br>tissue<br>supports<br>the<br>molecular<br>associatio<br>n but<br>does not<br>provide<br>direct<br>treatment<br>-outcome<br>validatio<br>n. |
| [24]<br>Wilso<br>n et<br>al.,<br>2008          | Review/p<br>erspectiv<br>e                                    | 5-<br>FU/nucle<br>otide<br>metabolis<br>m                          | Context<br>ual<br>evidenc<br>e only                       | Nucleotid<br>e-<br>metabolis<br>m and<br>treatment<br>-response<br>context.                                                                                                                                                                   | Cont<br>ext<br>only          | Not<br>applicable<br>for<br>grading in<br>this<br>review                                                                             | Not indepen<br>dently<br>apprais<br>ed for<br>grade                                                                                                                                    | Not inde<br>pend<br>ently<br>grad<br>ed | Backgrou<br>nd source<br>only.                                                                                                                                                                                                                                                                          |
| [25]<br>Strav<br>opodi<br>s et<br>al.,<br>2011 | Non-<br>CRC<br>bladder<br>cancer<br>cell study                | 5-FU/TS-<br>p53<br>apoptosis<br>context                            | Graded<br>supporti<br>ng<br>evidenc<br>e                  | TS<br>inhibition<br>can<br>trigger<br>p53-<br>dependen<br>t and<br>independ                                                                                                                                                                   | Parti<br>al/in<br>direc<br>t | Functional<br>perturbati<br>on in a<br>non-CRC<br>model.                                                                             | Non-<br>CRC<br>cell<br>model.                                                                                                                                                          | Indir<br>ect                            | Relevant<br>to<br>fluoropyr<br>imidine/p<br>53<br>biology,<br>but not<br>direct                                                                                                                                                                                                                         |

## Supplementary Table S1 and Supplementary Table S2

|                              |                                                                    |                             |                                         |                                                                                         |              |                                                                                                 |                                                                                    |                          |                                                                                                              |
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|                              |                                                                    |                             |                                         | ent apoptosis.                                                                          |              |                                                                                                 |                                                                                    |                          | evidence of acquired CRC chemoresistance.                                                                    |
| [26] Dominianni et al., 2018 | CRC cell study                                                     | 5-FU/p53-dependent response | Graded mechanistic/therapeutic evidence | p53 status alters fluoropyrimidine response.                                            | Yes          | Treatment-response comparison across p53 contexts.                                              | Cell models only.                                                                  | Limited                  | Direct CRC drug-response evidence without complementary organoid, in vivo or clinical validation.            |
| [27] Tae et al., 2026        | 5-FU-resistant CRC cells, patient-derived organoids and xenografts | Acquired 5-FU resistance    | Graded mechanistic/therapeutic evidence | EHMT2-PPM1B signalling supports 5-FU resistance; EHMT2 inhibition restores sensitivity. | Yes          | EHMT2 knockdown/pharmacological inhibition with sensitisation, cell-cycle and apoptosis assays. | Resistant CRC cells, PDOs, xenografts; patient-response association is supportive. | Moderate                 | Direct mechanism validated across complementary advanced models; therapeutic inhibition remains preclinical. |
| [28] Cai et al., 2025        | 5-FU-resistant CRC cell and in vivo models                         | 5-FU resistance             | Graded mechanistic/therapeutic evidence | UGDH promotes 5-FU resistance through ROS-PI3K/AKT-EEF1A2-PRDX1 signalling.             | Yes          | Stable knockdown/overexpression with ROS, apoptosis and 5-FU response assays.                   | In vitro and in vivo CRC models.                                                   | Moderate                 | Direct mechanistic perturbation with complementary in vivo validation.                                       |
| [29] Seetharam et al., 2009  | Review/contextual synthesis                                        | Oxaliplatin resistance      | Contextual evidence only                | Oxaliplatin-resistance background.                                                      | Context only | Not applicable for grading in this review                                                       | Not independently appraised for grade                                              | Not independently graded | Contextual secondary evidence only.                                                                          |
| [30] Alcindor et al., 2011   | Review/contextual synthesis                                        | Oxaliplatin mechanism       | Contextual evidence only                | Platinum pharmacology and resistance                                                    | Context only | Not applicable for grading in                                                                   | Not independently appraised                                                        | Not independently        | Contextual secondary                                                                                         |

## Supplementary Table S1 and Supplementary Table S2

|                                |                                                      |                                     |                                         | background.                                                                                                |              | this review                                                     | ed for grade                               | graded                   | evidence only.                                                                          |
|--------------------------------|------------------------------------------------------|-------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------|--------------|-----------------------------------------------------------------|--------------------------------------------|--------------------------|-----------------------------------------------------------------------------------------|
| [31]<br>Seetharam et al., 2010 | Oxaliplatin-resistant CRC cell models                | Oxaliplatin resistance              | Graded mechanistic/therapeutic evidence | ERCC1 upregulation contributes to oxaliplatin resistance.                                                  | Yes          | ERCC1 siRNA silencing restores oxaliplatin sensitivity.         | Cell models only.                          | Limited                  | Direct functional evidence, but restricted to cellular models.                          |
| [32]<br>Bohanes et al., 2011   | Review/contextual synthesis                          | Oxaliplatin/DNA repair              | Contextual evidence only                | DNA-repair-associated platinum-resistance context.                                                         | Context only | Not applicable for grading in this review                       | Not independently appraised for grade      | Not independently graded | Used for background synthesis only.                                                     |
| [33]<br>Kim et al., 2009       | Clinical CRC cohort                                  | 5-FU/oxaliplatin treatment response | Graded mechanistic/therapeutic evidence | ERCC1/TSG/STP expression is associated with treatment outcome.                                             | Yes          | Clinical association only.                                      | Human clinical cohort.                     | Limited                  | Direct human treatment association, but no functional mechanistic validation.           |
| [34]<br>Gao et al., 2026       | CRC cells, DTPs, organoids and in vivo tumour models | Oxaliplatin resistance              | Graded mechanistic/therapeutic evidence | LIG1-dependent repair limits oxaliplatin response; LIG1 targeting with gambogic acid restores sensitivity. | Yes          | LIG1 targeting, DNA-repair assays and chemosensitivity testing. | Cells, DTPs, organoids and in vivo models. | Moderate                 | Direct functional evidence reproduced across several complementary preclinical systems. |
| [35]<br>Lee et al., 2023       | CRC cell models                                      | Oxaliplatin response                | Graded mechanistic/therapeutic evidence | Glutathione depletion sensitises CRC cells to oxaliplatin.                                                 | Yes          | Pharmacological perturbation with chemosensitivity testing.     | Cell models only.                          | Limited                  | Direct functional support without complementary advanced-model validation.              |
| [36]<br>Pedraz-Cuesta et       | Drug-resistant CRC cell models                       | SN-38/oxaliplatin response          | Graded mechanistic/therapeutic          | Glutamate transport and glutathio                                                                          | Yes          | Transporter inhibition with drug-                               | Cell models only.                          | Limited                  | Direct cellular evidence but no complem                                                 |

## Supplementary Table S1 and Supplementary Table S2

|                                    |                                                    |                                      |                                         |                                                                                                 |     |                                                                                   |                                                              |          |                                                                                                    |
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| al., 2015                          |                                                    |                                      | evidence                                | ne availability influence oxaliplatin/SN-38-induced cell death.                                 |     | response assays.                                                                  |                                                              |          | entary organoid, in vivo or clinical validation.                                                   |
| [37] Fu et al., 2024               | Oxaliplatin-resistant CRC cells and in vivo models | Oxaliplatin resistance               | Graded mechanistic/therapeutic evidence | AKR1C1-STAT3 signalling raises glutathione and drives oxaliplatin resistance.                   | Yes | Genetic silencing and pharmacological inhibition restore oxaliplatin sensitivity. | Cell models plus in vivo resistant-tumour models.            | Moderate | Direct functional resistance mechanism with complementary in vivo validation.                      |
| [38] Buß et al., 2018              | CRC cell models                                    | Oxaliplatin uptake/resistance        | Graded mechanistic/therapeutic evidence | CTR1 and organic cation transporters influence oxaliplatin uptake and resistance.               | Yes | Transport/uptake and drug-response analyses.                                      | Cell models only.                                            | Limited  | Direct transporter evidence, but confined to cellular models.                                      |
| [39] Le Roy et al., 2016           | Clinical case-control study                        | FOLFOX-4/oxaliplatin response        | Graded mechanistic/therapeutic evidence | Tumour expression of oxaliplatin transporters is associated with response to adjuvant FOLFOX-4. | Yes | Clinical association; no experimental perturbation.                               | Human CRC treatment cohort.                                  | Limited  | Direct human treatment-response evidence, but mechanistic causality is not established.            |
| [40] Martinez-Bernabe et al., 2024 | CRC translational biomarker study                  | Oxaliplatin response/metabolic state | Graded mechanistic/therapeutic evidence | Oxidative-phosphorylation features are evaluated as predictors of oxaliplatin response.         | Yes | Biomarker/response analysis.                                                      | Translational evidence; mechanistic perturbation is limited. | Limited  | Relevant to treatment response, but functional validation of a resistance mechanism is incomplete. |

## Supplementary Table S1 and Supplementary Table S2

|                              |                                               |                                           |                                         |                                                                                   |              |                                                                         |                                                                  |                          |                                                                                                                                   |
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| [41]<br>Jeong et al., 2019   | Oxaliplatin-resistant CRC cell models         | Oxaliplatin resistance                    | Graded mechanistic/therapeutic evidence | Cannabidiol restores oxaliplatin response through NOS3/SOD2-associated autophagy. | Yes          | Pharmacological treatment with mechanistic and chemosensitivity assays. | Predominantly cell-based evidence.                               | Limited                  | Direct resistance-reversal evidence, but complementary organoid/in vivo/clinical validation is limited in the evidence used here. |
| [42]<br>Thomas et al., 2019  | Review                                        | Irinotecan resistance                     | Contextual evidence only                | TOP1/irinotecan therapeutic background.                                           | Context only | Not applicable for grading in this review                               | Not independently appraised for grade                            | Not independently graded | Contextual review only.                                                                                                           |
| [43]<br>Ozawa et al., 2021   | Review/contextual synthesis                   | Irinotecan resistance                     | Contextual evidence only                | Cellular irinotecan resistance and therapeutic combination context.               | Context only | Not applicable for grading in this review                               | Not independently appraised for grade                            | Not independently graded | Review article; did not independently contribute to an evidence grade.                                                            |
| [44]<br>Gongora et al., 2011 | Camptothecin-resistant cancer cell models     | TOP1-mediated irinotecan-class resistance | Graded mechanistic/therapeutic evidence | TOP1 mutations are associated with resistance to camptothecin-class agents.       | Partial      | Resistant-model molecular characterization.                             | Predominantly cell models; not a complementary CRC model series. | Limited                  | Direct target-based resistance evidence, but limited model breadth and CRC-specific translational validation.                     |
| [45]<br>Jensen et al., 2016  | SN-38-resistant human colon cancer cell lines | Irinotecan/SN-38 resistance               | Graded mechanistic/therapeutic evidence | Resistance-associated TOP1 mutations occur in SN-38-resistant colon               | Yes          | Established acquired-resistant cell models with TOP1 characterization.  | Cell models only.                                                | Limited                  | Direct acquired-resistance evidence without organoid, in vivo or clinical                                                         |

## Supplementary Table S1 and Supplementary Table S2

|                              |                                |                                  |                                         |                                                                                |                  |                                           |                                       |                          |                                                                                                                                                                 |
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|                              |                                |                                  |                                         | cancer cells.                                                                  |                  |                                           |                                       |                          | validation.                                                                                                                                                     |
| [46]<br>Nielsen et al., 2017 | Review                         | ABCG2/irinotecan                 | Contextual evidence only                | Context for transporter-mediated irinotecan response.                          | Context only     | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Review article used for contextual synthesis only.                                                                                                              |
| [47]<br>de Man et al., 2018  | Review/contextual synthesis    | Irinotecan pharmacology          | Contextual evidence only                | Pharmacokinetic, pharmacodynamic and pharmacogenetic context for irinotecan.   | Context only     | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Review article; did not independently increase a mechanistic evidence grade.                                                                                    |
| [48]<br>Wang et al., 2012    | Clinical CRC cohort            | Irinotecan/5-FU pharmacogenetics | Graded mechanistic/therapeutic evidence | UGT1A1 genotype is associated with outcomes during irinotecan-based treatment. | Partial          | Clinical association only.                | Human treatment cohort.               | Indirect                 | Clinically relevant to irinotecan exposure/outcome, but does not directly establish tumour-cell acquired resistance.                                            |
| [49]<br>Jossé et al., 2014   | Cancer cell and in vivo models | TOP1-inhibitor response          | Graded supporting evidence              | ATR inhibition increases sensitivity to TOP1 inhibition/irinotecan.            | Partial/indirect | Pharmacological ATR inhibition.           | In vivo validation.                   | Indirect                 | Evidence is extrapolated from a related biological/treatment context rather than directly demonstrating the specific acquired CRC pathway-resistance mechanism. |

## Supplementary Table S1 and Supplementary Table S2

|                            |                                                         |                              |                                         |                                                                                                    |              |                                                                     |                                                                     |                          |                                                                                                                                             |
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| [50]<br>Manic et al., 2021 | Primary CRC stem-cell and in vivo models                | Replication-stress survival  | Graded mechanistic/therapeutic evidence | PARP1-MRE11-RAD51 programmes support replication-stress tolerance in CRC stem cells.               | Partial      | PARP1/MRE11/RAD51 perturbation with sensitisation assays.           | Primary CRC stem-cell models with complementary functional testing. | Indirect                 | Strong CRC replication-stress biology, but no direct demonstration of the specific irinotecan/Wnt/Notch/YAP relationship graded in Table 2. |
| [51]<br>Lin et al., 2025   | FBW7-deficient CRC cells, patient tissue and xenografts | Irinotecan/SN-38 resistance  | Graded mechanistic/therapeutic evidence | FBW7 deficiency stabilises MCL1 and drives irinotecan resistance; maritoclax restores sensitivity. | Yes          | CRISPR/RNAi, MCL1 manipulation and pharmacological resensitisation. | CRC patient tissue plus in vivo xenografts.                         | Moderate                 | Direct mechanism with complementary in vivo and supportive human tissue evidence; the therapeutic intervention remains preclinical.         |
| [52]<br>Chen et al., 2022  | Mini-review                                             | CRC CSC chemoresistance      | Contextual evidence only                | CSC-related chemoresistance context                                                                | Context only | Not applicable for grading in this review                           | Not independently appraised for grade                               | Not independently graded | Secondary contextual source only.                                                                                                           |
| [53]<br>Begic et al., 2017 | Review                                                  | ABC transporters/CSCs        | Contextual evidence only                | ABC-transporter contribution to CSC drug resistance.                                               | Context only | Not applicable for grading in this review                           | Not independently appraised for grade                               | Not independently graded | Secondary contextual source only.                                                                                                           |
| [54]<br>Hsu et al., 2018   | Oxaliplatin-resistant CRC cell models                   | Oxaliplatin/cross-resistance | Graded mechanistic/therapeutic evidence | ABCG2 activation reduces ER-stress-mediated apoptosis and contribute                               | Yes          | ABCG2/pathway manipulation and chemosensitivity testing.            | Cell models only.                                                   | Limited                  | Direct functional evidence, but no higher-order                                                                                             |

## Supplementary Table S1 and Supplementary Table S2

|                                 |                                                                      |                              |                                         |                                                                          |              |                                                                        |                                                               |                          |                                                                                                                                                                                       |
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|                                 |                                                                      |                              |                                         | s to oxaliplatin resistance.                                             |              |                                                                        |                                                               |                          | validation.                                                                                                                                                                           |
| [55] Zhong et al., 2024         | Review                                                               | CRC stem cells               | Contextual evidence only                | CSC contribution to drug resistance                                      | Context only | Not applicable for grading in this review                              | Not independently appraised for grade                         | Not independently graded | Secondarily contextual source only.                                                                                                                                                   |
| [56] Garza-Treviño et al., 2015 | Review                                                               | Colon CSCs                   | Contextual evidence only                | CSC biology and therapeutic context                                      | Context only | Not applicable for grading in this review                              | Not independently appraised for grade                         | Not independently graded | Secondarily contextual source only.                                                                                                                                                   |
| [57] Escalante et al., 2021     | Review                                                               | EMT/FO LFOX resistance       | Contextual evidence only                | EMT-associated resistance context                                        | Context only | Not applicable for grading in this review                              | Not independently appraised for grade                         | Not independently graded | Secondarily contextual source only.                                                                                                                                                   |
| [58] Sun et al., 2017           | CRC cell lines plus chemotherapy-treated stage II/III patient cohort | 5-FU resistance ; Notch/HES1 | Graded mechanistic/therapeutic evidence | HES1 promotes 5-FU resistance through EMT and ABC-transporter induction. | Yes          | HES1 overexpression/inhibition with cytotoxicity and molecular assays. | Human adjuvant-chemotherapy cohort linked HES1 to recurrence. | Limited                  | Direct functional evidence in CRC cell models with supportive retrospective clinical association, but the human data do not directly validate HES1-mediated 5-FU resistance causally. |
| [59] Jiang et al., 2017         | Review                                                               | EMT/ABC transporters         | Contextual evidence only                | EMT-transporter relationship                                             | Context only | Not applicable for grading in this review                              | Not independently appraised for grade                         | Not independently graded | Secondarily contextual source only.                                                                                                                                                   |
| [60] Fodde, 2002                | Review                                                               | APC                          | Contextual evidence only                | APC biology in CRC                                                       | Context only | Not applicable for grading in                                          | Not independently appraised                                   | Not independently        | Foundational background                                                                                                                                                               |

## Supplementary Table S1 and Supplementary Table S2

|                                 |                                                             |                                            |                                            |                                                                        |               | this review                                                   | ed for grade                             | grad ed                     | nd source only.                                                                         |
|---------------------------------|-------------------------------------------------------------|--------------------------------------------|--------------------------------------------|------------------------------------------------------------------------|---------------|---------------------------------------------------------------|------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------|
| [61]<br>Schat off et al., 2017  | Review                                                      | Wnt/CRC                                    | Context ual evidenc e only                 | Canonical Wnt pathway backgrou nd                                      | Cont ext only | Not applicable for grading in this review                     | Not indepen dently apprais ed for grade  | Not inde pend ently grad ed | Foundati onal backgrou nd source only.                                                  |
| [62]<br>Hank ey et al., 2018    | Review                                                      | APC/Wnt                                    | Context ual evidenc e only                 | APC-dependen t and independ ent signalling                             | Cont ext only | Not applicable for grading in this review                     | Not indepen dently apprais ed for grade  | Not inde pend ently grad ed | Backgrou nd source only.                                                                |
| [63]<br>He et al., 1998         | Foundati onal mechanis tic study                            | c-MYC/Wnt                                  | Context ual evidenc e only                 | Establishe s c-MYC as an APC/ $\beta$ -catenin target                  | Cont ext only | Not applicable for resistance grading                         | Not indepen dently apprais ed for grade  | Not inde pend ently grad ed | Foundati onal pathway evidence, not acquired chemores istance.                          |
| [64]<br>Shtut man et al., 1999  | Foundati onal mechanis tic study                            | Cyclin D1/Wnt                              | Context ual evidenc e only                 | Establishe s cyclin D1 as a $\beta$ -catenin target                    | Cont ext only | Not applicable for resistance grading                         | Not indepen dently apprais ed for grade  | Not inde pend ently grad ed | Foundati onal pathway evidence, not acquired chemores istance.                          |
| [65]<br>Brabl etz et al., 2000  | Human patholog y study                                      | $\beta$ -catenin/c-MYC                     | Context ual evidenc e only                 | Human CRC Wnt-expressio n context                                      | Cont ext only | Not applicable for resistance grading                         | Human tumour specime ns                  | Not inde pend ently grad ed | Provides pathway context rather than evidence for a specific acquired resistance claim. |
| [66]<br>Chika zawa et al., 2010 | Chemoth erapy-resistant side-populatio n colon cancer cells | Wnt-associate d multidrug resistance       | Graded mechanis tic/ther apeutic evidenc e | Wnt inhibition reduces chemothe rapy-resistant side-populatio n cells. | Yes           | Wnt-pathway inhibition with resistant-population assessmen t. | Cell models only.                        | Limi ted                    | Direct pathway-related evidence, but limited to cellular models.                        |
| [67]<br>Liu et al., 2021        | CRC cells, in vivo models and chemores istant               | Wnt/stem ness-associate d chemores istance | Graded mechanis tic/ther apeutic evidenc e | Sec62 promotes CRC stemness and chemoresi stance                       | Yes           | Sec62 depletion/overexpres sion and pathway assays.           | In vivo models and human chemor esistant | Stron g                     | Functiona l mechanis m supporte d by complem                                            |

## Supplementary Table S1 and Supplementary Table S2

|                          |                                             |                                           |                                         |                                                                                                          |                  |                                                     |                                                                                                |          |                                                                                                             |
|--------------------------|---------------------------------------------|-------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------|------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------|----------|-------------------------------------------------------------------------------------------------------------|
|                          | human CRC tissues                           |                                           |                                         | through Wnt/ $\beta$ -catenin signalling .                                                               |                  |                                                     | CRC tissue.                                                                                    |          | entary in vivo and direct human chemoresistance evidence.                                                   |
| [68] Chen et al., 2019   | CRC experimental study                      | Wnt/stemness context                      | Graded supporting evidence              | miR-103/107 prolongs Wnt/ $\beta$ -catenin signalling and CRC stemness via AXIN2.                        | Partial/indirect | Genetic manipulation.                               | Experimental CRC models; no direct acquired drug-resistance demonstration.                     | Indirect | Supports Wnt/stemness biology, but not a specific acquired chemotherapy-resistance mechanism.               |
| [69] Stein et al., 2012  | Colon cancer cell and human tumour analysis | $\beta$ -catenin/ABC1 drug-efflux biology | Graded mechanistic/therapeutic evidence | Mutant $\beta$ -catenin regulates ABC1 expression.                                                       | Partial          | $\beta$ -catenin manipulation and promoter studies. | Human tumour expression analysis ; drug-specific resistance effect was not firmly established. | Indirect | Mechanistic ABC1 regulation is shown, but the specific irinotecan-resistance relationship remains indirect. |
| [70] Wang et al., 2015   | 5-FU-resistant CRC cell models              | 5-FU resistance                           | Graded mechanistic/therapeutic evidence | TRPC5/Wnt-associated signalling contributes to 5-FU resistance and its inhibition restores sensitivity . | Yes              | TRPC5 inhibition with 5-FU resensitisation assays.  | Predominantly cell models.                                                                     | Limited  | Direct functional drug-resistance evidence without complementary advanced-model validation.                 |
| [71] Lapham et al., 2009 | CRC cell study                              | Wnt/apoptosis context                     | Graded supporting evidence              | $\beta$ -catenin/TCF4 transcriptionally activates BCL-W.                                                 | Partial/indirect | Promoter/pathway manipulation.                      | Cell models only.                                                                              | Indirect | Establishes Wnt-BCL-W biology, but not direct acquired 5-FU resistance .                                    |

## Supplementary Table S1 and Supplementary Table S2

|                            |                                                              |                                              |                                         |                                                                                                             |                   |                                                                                                    |                                                     |                          |                                                                                                                                                          |
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| [72]<br>Pate et al., 2014  | CRC metabolic /pathway study                                 | Wnt/metabolic adaptation context             | Graded supporting evidence              | Wnt signalling directs glycolytic /angiogenic metabolic programmes.                                         | Partial/in direct | Wnt/metabolic manipulation.                                                                        | Experimental CRC models.                            | Indirect                 | Supports metabolic consequences of Wnt, not a drug-specific acquired-resistance phenotype.                                                               |
| [73]<br>Wang et al., 2017  | CRC cell and clinical tissue association study               | 5-FU chemoresistance/metabolic adaptation    | Graded mechanistic/therapeutic evidence | TRPC5 and GLUT1 expression is associated with CRC chemoresistance.                                          | Yes               | Expression and treatment-response association ; mechanistic perturbation is limited in this paper. | Human CRC tissue association.                       | Limited                  | Human association supports relevance, but direct functional causality is incomplete.                                                                     |
| [74]<br>Yuan et al., 2020  | Review                                                       | Wnt/CRC resistance                           | Contextual evidence only                | Wnt-associated stemness and treatment-survival context.                                                     | Context only      | Not applicable for grading in this review                                                          | Not independently appraised for grade               | Not independently graded | Used for contextual/background support only.                                                                                                             |
| [75]<br>Ayadi et al., 2015 | Multiple acquired chemotherapy-resistant CRC cell lines      | Chronic chemotherapy/Wnt-stemness adaptation | Graded mechanistic/therapeutic evidence | Chronic chemotherapy stress can alter stemness and Wnt/ $\beta$ -catenin signalling in resistant CRC cells. | Yes               | Long-term acquired-resistance models with pathway inhibition.                                      | Cell models only.                                   | Limited                  | Direct acquired-resistance modelling, but pathway inhibition did not establish a universal Wnt dependency and no advanced-model validation was provided. |
| [76]<br>Touil et al., 2014 | Acquired 5-FU-resistant CRC cells plus human post-5-FU liver | 5-FU quiescent /DTP-like survival; c-Yes/YAP | Graded mechanistic/therapeutic evidence | c-Yes/YAP-associated reversible quiescence supports survival                                                | Yes               | YES1/YAP functional manipulation and treatment/re-exposure analysis.                               | Human liver metastases after 5-FU-based neoadjuvant | Limited                  | Direct functional evidence for a reversible treatment-surviving                                                                                          |

## Supplementary Table S1 and Supplementary Table S2

|                        |                                                                  |                                   |                                         |                                                                               |     |                                                                  |                                                     |          |                                                                                                                                                                                             |
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|                        | metastases                                                       |                                   |                                         | after 5-FU and relates to relapse.                                            |     |                                                                  | chemotherapy.                                       |          | state with supportive treatment-exposed human material, but the human evidence does not directly establish c-YAP1-mediated reversible quiescence as a stable acquired-resistance mechanism. |
| [77] Park et al., 2021 | CRC cells, mouse models and patient tumours after chemoradiation | Wnt-associated therapy resistance | Graded mechanistic/therapeutic evidence | CD45-Wnt signalling promotes stemness and survival after 5-FU/chemoradiation. | Yes | CD45 depletion and pathway assays with therapy-response testing. | Mouse models and human pretreated tumour specimens. | Strong   | Functional mechanism with direct validation in treatment-exposed human CRC material.                                                                                                        |
| [78] He et al., 2018   | 5-FU-resistant CRC cell and xenograft models                     | 5-FU/Wnt resistance               | Graded mechanistic/therapeutic evidence | Wnt/ $\beta$ -catenin-CHK1 signalling contributes to 5-FU resistance.         | Yes | Wnt and CHK1 manipulation with chemosensitivity testing.         | In vivo xenograft validation.                       | Moderate | Direct functional evidence with complementary in vivo validation; no human or clinical validation.                                                                                          |
| [79] Liu et al., 2021  | CRC cells and xenografts                                         | Oxaliplatin resistance            | Graded mechanistic/therapeutic evidence | SOX9-MMS22L-dependent DNA repair promotes oxaliplatin                         | Yes | SOX9/MM22L overexpression/knockdown, DNA-repair and              | In vivo xenograft validation; human CRC             | Moderate | Direct functional mechanism with complementary in                                                                                                                                           |

## Supplementary Table S1 and Supplementary Table S2

|                            |                                                          |                                        |                                         |                                                                                             |              |                                                                        |                                       |                          |                                                                                                        |
|----------------------------|----------------------------------------------------------|----------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------|--------------|------------------------------------------------------------------------|---------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------|
|                            |                                                          |                                        |                                         | n resistance.                                                                               |              | chemosensitivity assays.                                               | expression/prognostic association.    |                          | vivo validation; human data are supportive rather than direct treatment-validation.                    |
| [80] Huang et al., 2024    | Oxaliplatin-resistant CRC models with in vivo validation | Oxaliplatin resistance                 | Graded mechanistic/therapeutic evidence | Wnt/ $\beta$ -catenin-IMPDH2-driven purine metabolism promotes oxaliplatin resistance.      | Yes          | Wnt/IMPDH2 manipulation, metabolic rescue and chemosensitivity assays. | Complementary in vivo CRC models.     | Moderate                 | Direct functional mechanism reproduced beyond cell culture.                                            |
| [81] Betson et al., 2022   | Multiple CRC cell lines                                  | Chemotherapy response/ABC transporters | Graded mechanistic/therapeutic evidence | IGF2BP1 supports ABCB1/ABCG2 expression and chemoresistance, including irinotecan response. | Yes          | IGF2BP1 knockdown with chemosensitivity/apoptosis assays.              | Cell models only.                     | Limited                  | Direct functional evidence but no organoid, in vivo or human validation.                               |
| [82] Shah et al., 2021     | Review                                                   | PORCN inhibitors                       | Contextual evidence only                | Wnt-targeted therapeutic context                                                            | Context only | Not applicable for grading in this review                              | Not independently appraised for grade | Not independently graded | Secondary contextual source only.                                                                      |
| [83] Rodon et al., 2021    | Phase I study                                            | WNT974                                 | Contextual evidence only                | Clinical Wnt-inhibitor safety/activity context                                              | Context only | Not applicable for resistance grading                                  | Human phase I trial                   | Not independently graded | Used to establish pathway-targeting feasibility rather than acquired chemotherapy-resistance evidence. |
| [84] Flanagan et al., 2022 | Review                                                   | PORCN inhibition                       | Contextual evidence only                | Ligand-dependent Wnt targeting                                                              | Context only | Not applicable for grading in                                          | Not independently appraised           | Not independently        | Secondary contextual source only.                                                                      |

## Supplementary Table S1 and Supplementary Table S2

|                              |                               |                              |                            |                                                                    |                   | this review                               | ed for grade                          | graded                   |                                                                                                  |
|------------------------------|-------------------------------|------------------------------|----------------------------|--------------------------------------------------------------------|-------------------|-------------------------------------------|---------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------|
| [85] Mada n et al., 2016     | Preclinical cancer study      | Wnt-targeted therapy context | Graded supporting evidence | PORCN inhibition suppresses ligand-dependent Wnt-driven tumours.   | Partial/in direct | Pharmacological Wnt inhibition.           | In vivo models.                       | Indirect                 | Pathway-targeting evidence without direct acquired CRC chemotherapy-resistance modelling.        |
| [86] Bond et al., 2016       | Human CRC molecular study     | Wnt-targeting stratification | Graded supporting evidence | RNF43/ZNFR3 alterations define ligand-dependent Wnt contexts.      | Partial/in direct | Molecular association.                    | Human tumours.                        | Indirect                 | Relevant to pathway stratification, not direct acquired chemoresistance.                         |
| [87] Huels et al., 2018      | Intestinal /CRC in vivo study | Wnt biology/targeting        | Graded supporting evidence | Wnt ligands influence tumour initiation and stem-cell competition. | Partial/in direct | Genetic/pathway manipulation.             | In vivo models.                       | Indirect                 | Supports pathway biology and targeting limitations rather than acquired chemotherapy resistance. |
| [88] Taber nero et al., 2023 | Phase Ib/II study             | WNT974 combinations          | Contextual evidence only   | Clinical Wnt-targeting context                                     | Context only      | Not applicable for resistance grading     | Human clinical trial                  | Not independently graded | Used for clinical pathway-targeting context, not direct acquired chemoresistance evidence.       |
| [89] Nach ef et al., 2026    | Review                        | Wnt inhibitors               | Contextual evidence only   | Bone/on-target toxicity                                            | Context only      | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Secondarily contextual source only.                                                              |
| [90] Shin et al., 2017       | CRC in vitro/in vivo study    | Wnt-targeted therapy         | Graded supporting evidence | $\beta$ -catenin-TCF4 inhibition suppresses                        | Partial/in direct | Direct pathway inhibition.                | Cell and in vivo models.              | Indirect                 | Demonstrates Wnt druggability but not                                                            |

## Supplementary Table S1 and Supplementary Table S2

|                          |                                                                                     |                                           |                                         |                                                                                                                  |                  |                                                                             |                                                         |                          |                                                                                                                              |
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|                          |                                                                                     |                                           |                                         | s CRC growth.                                                                                                    |                  |                                                                             |                                                         |                          | acquired chemotherapy resistance.                                                                                            |
| [91] Tanton et al., 2022 | CRC preclinical study                                                               | Wnt-targeted therapy                      | Graded supporting evidence              | $\beta$ -catenin/BCL9 inhibition suppresses oncogenic Wnt signalling.                                            | Partial/indirect | Pharmacological pathway inhibition.                                         | Preclinical CRC models.                                 | Indirect                 | Therapeutic pathway evidence without direct acquired chemotherapy-resistance modelling.                                      |
| [92] Chen et al., 2023   | Review                                                                              | Wnt targeting                             | Contextual evidence only                | Strategies for Wnt inhibition in CRC                                                                             | Context only     | Not applicable for grading in this review                                   | Not independently appraised for grade                   | Not independently graded | Secondarily contextual source only.                                                                                          |
| [93] Kahn, 2014          | Review                                                                              | Wnt safety                                | Contextual evidence only                | Safety limitations of Wnt targeting                                                                              | Context only     | Not applicable for grading in this review                                   | Not independently appraised for grade                   | Not independently graded | Secondarily contextual source only.                                                                                          |
| [94] Ji et al., 2022     | Translational modelling                                                             | WNT974                                    | Contextual evidence only                | Dose-selection/translational context                                                                             | Context only     | Not applicable for resistance grading                                       | Translational pharmacological modelling                 | Not independently graded | Used for Wnt-inhibitor development context rather than a resistance claim.                                                   |
| [95] Cho et al., 2020    | Mouse CRC models, patient-derived tumour organoids and patient-derived tumour cells | 5-FU-induced stemness/tumour repopulation | Graded mechanistic/therapeutic evidence | 5-FU activates p53-WNT3- $\beta$ -catenin signalling, enriching residual stem-like cells and promoting regrowth. | Yes              | Pathway manipulation and Wnt inhibition with treatment/withdrawal response. | Mouse models plus patient-derived organoid/cell models. | Moderate                 | Direct functional chemotherapy-adaptation evidence across complementary advanced models; no prospective clinical validation. |

## Supplementary Table S1 and Supplementary Table S2

|                               |                                                                          |                                                                |                                         |                                                                                                                                                                                            |                   |                                                                                                            |                                                                                    |                          |                                                                                                                                                                             |
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| [96]<br>Wang et al., 2018     | Acquired 5-FU-resistant CRC cells plus human chemotherapy-outcome cohort | 5-FU resistance ; TRPC5/G LUT1-dependent glycolytic adaptation | Graded mechanistic/therapeutic evidence | Enhanced glycolysis supports TRPC5-associated 5-FU resistance; glycolysis inhibition reverses resistance, and high TRPC5/G LUT1 expression is associated with poorer chemotherapy outcome. | Yes               | TRPC5 knockdown and pharmacological glycolysis inhibition with ATP, apoptosis and 5-FU sensitivity assays. | 5-FU-resistant CRC cell models plus human CRC tissue/clinical outcome association. | Strong                   | Direct functional 5-FU-resistance evidence with concordant human chemotherapy-outcome association, although the clinical evidence is observational rather than prospective. |
| [97]<br>Tyagi et al., 2020    | Review/contextual synthesis                                              | Notch/CRC                                                      | Contextual evidence only                | Notch-associated stemness, survival and therapeutic context.                                                                                                                               | Context only      | Not applicable for grading in this review                                                                  | Not independently appraised for grade                                              | Not independently graded | Used for contextual/background support only.                                                                                                                                |
| [98]<br>van Es et al., 2005   | Foundational study                                                       | Notch                                                          | Contextual evidence only                | Intestinal differentiation and Notch biology                                                                                                                                               | Context only      | Not applicable for grading in this review                                                                  | Not independently appraised for grade                                              | Not independently graded | Foundational pathway context.                                                                                                                                               |
| [99]<br>Sikandar et al., 2010 | Experimental/contextual source                                           | Notch/CS C                                                     | Contextual evidence only                | Tumour-initiating-cell and differentiation biology                                                                                                                                         | Context only      | Not applicable for resistance grading                                                                      | Experimental CRC models                                                            | Not independently graded | Used to establish Notch/CS C biology rather than direct chemotherapy resistance.                                                                                            |
| [100]<br>Lu et al., 2013      | CRC endothelial/stem-cell experimental study                             | Notch/TME stemness                                             | Graded supporting evidence              | Endothelial Jagged1 promotes a CRC stem-cell phenotype.                                                                                                                                    | Partial/in direct | Jagged1/Notch functional manipulation.                                                                     | Experimental/in vivo CRC models.                                                   | Indirect                 | Supports TME-Notch stemness biology, not a direct acquired chemotherapy                                                                                                     |

## Supplementary Table S1 and Supplementary Table S2

|                              |                                           |                     |                            |                                                                    |                  |                                           |                                       |                          |                                                                                |
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|                              |                                           |                     |                            |                                                                    |                  |                                           |                                       |                          | rapy-resistance mechanism.                                                     |
| [101] Radu et al., 2024      | Review                                    | CRC CSCs            | Contextual evidence only   | Cancer-stem-cell context                                           | Context only     | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Secondary source only.                                                         |
| [102] Fendler et al., 2015   | CRC cell study                            | Notch/EMT/stemness  | Graded supporting evidence | Notch1 promotes stemness and EMT in CRC.                           | Partial/indirect | Notch manipulation.                       | Cell models.                          | Indirect                 | Adaptive-state biology without drug-specific acquired resistance.              |
| [103] Pal et al., 2018       | Metastatic colon cancer preclinical study | Notch/AKT/EMT       | Graded supporting evidence | Notch1/AKT inhibition suppresses EMT.                              | Partial/indirect | Functional pathway inhibition.            | Preclinical models.                   | Indirect                 | Related pathway evidence without direct chemotherapy-resistance demonstration. |
| [104] Vermeylen et al., 2010 | CRC stem-cell translational study         | Wnt/stemness        | Graded supporting evidence | Wnt activity defines colon CSCs and is microenvironment-regulated. | Partial/indirect | Functional stem-cell assays.              | Human/in vivo support.                | Indirect                 | Foundational stemness evidence, not direct acquired chemotherapy resistance.   |
| [105] Rodilla et al., 2009   | CRC experimental study                    | Wnt-Notch crosstalk | Graded supporting evidence | Jagged1 links Wnt and Notch pathways in CRC.                       | Partial/indirect | Genetic/pathway manipulation.             | Preclinical CRC models.               | Indirect                 | Establishes pathway crosstalk but not a drug-specific resistance phenotype.    |
| [106] Pannequin et al., 2009 | CRC cell study                            | Wnt-Notch crosstalk | Graded supporting evidence | Wnt target Jagged1 mediates Notch activation by                    | Partial/indirect | Pathway manipulation.                     | Cell models.                          | Indirect                 | Mechanistic crosstalk evidence without direct acquired                         |

## Supplementary Table S1 and Supplementary Table S2

|                                     |                                                               |                              |                                         |                                                                                                                      |              |                                                                                 |                                                                                      |                          |                                                                                                                                                                                                                     |
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|                                     |                                                               |                              |                                         | progastrin.                                                                                                          |              |                                                                                 |                                                                                      |                          | chemoresistance.                                                                                                                                                                                                    |
| [107] Bertrاند et al., 2012         | Review                                                        | Developmental pathways       | Contextual evidence only                | Wnt/Notch/BMP/Hedgehog crosstalk                                                                                     | Context only | Not applicable for grading in this review                                       | Not independently appraised for grade                                                | Not independently graded | Secondarily contextual source only.                                                                                                                                                                                 |
| [108] Meng et al., 2009             | Colon cancer cell models                                      | Oxaliplatin/Notch adaptation | Graded mechanistic/therapeutic evidence | Oxaliplatin activates Notch1; $\gamma$ -secretase inhibition enhances chemosensitivity.                              | Yes          | $\gamma$ -secretase inhibition and NICD manipulation with drug-response assays. | Cell models only.                                                                    | Limited                  | Direct drug-specific functional evidence without organoid, in vivo or clinical validation.                                                                                                                          |
| [109] Wang et al., 2020             | CRC cells, human CRC specimens and patient-derived xenografts | Oxaliplatin resistance       | Graded mechanistic/therapeutic evidence | Low H3K27me3/NOTCH2-associated adaptation contributes to oxaliplatin resistance and can be therapeutically reversed. | Yes          | Epigenetic manipulation with apoptosis/chemosensitivity assays.                 | Human chemotherapeutic outcome association and oxaliplatin-resistant PDX validation. | Moderate                 | Direct functional resistance evidence with complementary PDX validation; the human chemotherapeutic outcome association is supportive but does not constitute direct clinical validation of the proposed mechanism. |
| [110] Mouillet-Richard et al., 2020 | Review                                                        | YAP/TAZ                      | Contextual evidence only                | YAP/TAZ and CRC molecular subtypes                                                                                   | Context only | Not applicable for grading in this review                                       | Not independently appraised for grade                                                | Not independently graded | Secondarily contextual source only.                                                                                                                                                                                 |
| [111] Zinatizadeh                   | Review                                                        | Hippo/YAP                    | Contextual                              | Hippo pathway and                                                                                                    | Context only | Not applicable for                                                              | Not independently                                                                    | Not independently        | Secondarily contextual                                                                                                                                                                                              |

## Supplementary Table S1 and Supplementary Table S2

|                               |                                                        |                               |                                         |                                                                        |              |                                                                                          |                                                                         |                          |                                                                                                                              |
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| et al., 2019                  |                                                        |                               | evidence only                           | cancer progression                                                     |              | grading in this review                                                                   | appraised for grade                                                     | entirely graded          | 1 source only.                                                                                                               |
| [112] Mohamdpour et al., 2024 | Review                                                 | Hippo/CRC                     | Contextual evidence only                | Hippo signalling and therapeutic potential                             | Context only | Not applicable for grading in this review                                                | Not independently appraised for grade                                   | Not independently graded | Secondarily contextual source only.                                                                                          |
| [113] Huang et al., 2020      | Acquired 5-FU-resistant CRC cells and xenograft models | 5-FU resistance               | Graded mechanistic/therapeutic evidence | Combined EGFR and YAP inhibition reverses 5-FU resistance.             | Yes          | YAP/EGFR inhibition with chemosensitivity assays.                                        | Cell models plus in vivo xenografts; no direct clinical validation.     | Moderate                 | Direct functional resistance mechanism reproduced in vitro and in vivo.                                                      |
| [114] Yang et al., 2025       | Oxaliplatin-resistant CRC cells and xenografts         | Oxaliplatin/YAP resistance    | Graded mechanistic/therapeutic evidence | EDN1- $\beta$ -arrestin1-YAP signalling drives oxaliplatin resistance. | Yes          | EDN1 knockdown/overexpression and YAP-pathway manipulation with chemosensitivity assays. | In vivo xenograft validation; human survival association is supportive. | Moderate                 | Direct functional mechanism with complementary in vivo validation; human data do not directly validate treatment resistance. |
| [115] Xu et al., 2024         | CRC cells, xenografts and human CRC tissue             | 5-FU/YAP metabolic resistance | Graded mechanistic/therapeutic evidence | YAP promotes 5-FU chemoresistance through the mTOR-GLUT3 axis.         | Yes          | YAP/mTOR/GLUT3 manipulation with chemosensitivity and metabolic assays.                  | In vivo xenografts; human tissue/prognostic association.                | Moderate                 | Direct functional mechanism with in vivo validation; human evidence is supportive rather than treatment-specific.            |
| [116] Kim et al., 2026        | 5-FU- and oxaliplatin-resistant                        | YAP-linked chemoresistance    | Graded mechanistic/therapeutic evidence | AMOT-p80 supports YAP-dependence                                       | Yes          | AMOT depletion, isoform re-expression/rescue and YAP                                     | Cell models only.                                                       | Limited                  | Strong cell-level causality, but no organoid, in vivo or                                                                     |

## Supplementary Table S1 and Supplementary Table S2

|                              |                                              |                                          |                                         |                                                                     |                   |                                                              |                                       |                          |                                                                                                                 |
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|                              | CRC cell models                              |                                          |                                         | resistance to 5-FU and oxaliplatin.                                 |                   | manipulation.                                                |                                       |                          | human validation.                                                                                               |
| [117] Nguyen et al., 2019    | Review                                       | Notch/Hippo-YAP and resistance           | Contextual evidence only                | General signalling and resistance context.                          | Context only      | Not applicable for grading in this review                    | Not independently appraised for grade | Not independently graded | Used for contextual/background support only.                                                                    |
| [118] Zeng et al., 2021      | Review                                       | Hippo/drug resistance                    | Contextual evidence only                | YAP/TAZ drug-resistance context                                     | Context only      | Not applicable for grading in this review                    | Not independently appraised for grade | Not independently graded | Secondarily contextual source only.                                                                             |
| [119] Ogasawara et al., 2024 | CRC tumour-line study                        | YAP/plasticity                           | Graded supporting evidence              | Non-genomic drivers modulate YAP signalling and CRC plasticity.     | Partial/in direct | Molecular perturbation/characterisation.                     | CRC tumour-line models.               | Indirect                 | Supports plasticity/YAP biology, but not a specific cytotoxic drug-resistance mechanism.                        |
| [120] Brossseau et al., 2025 | Lung cancer experimental study               | YAP/chemoresistance cross-cancer context | Graded supporting evidence              | YAP/TEAD contribute to paclitaxel resistance.                       | Partial/in direct | Functional pathway studies.                                  | Non-CRC model.                        | Indirect                 | Cross-cancer chemotherapy evidence only.                                                                        |
| [121] Edwards et al., 2023   | Cancer/CRC targeted-therapy study            | KRASG12C inhibitor resistance            | Graded supporting evidence              | YAP1/TAZ drives primary/acquired resistance to KRASG12C inhibition. | Partial/in direct | TEAD/YAP pathway inhibition and resistance assays.           | Targeted-therapy context.             | Indirect                 | Resistance biology is relevant to adaptive signalling, but treatment context is not cytotoxic CRC chemotherapy. |
| [122] Xiang et al., 2025     | CRC organoids and patient-derived orthotopic | FOLFOX adaptive resistance               | Graded mechanistic/therapeutic evidence | ADAM10 - NOTCH2 -TCF7L2-mediated Wnt transcription                  | Yes               | Genetic/pharmacological pathway disruption and chemotherapy- | Organoid and PDOX validation.         | Moderate                 | Direct functional mechanism reproduced across comple                                                            |

## Supplementary Table S1 and Supplementary Table S2

|                               |                                         |                                      |                            |                                                                                                                                                                     |                  |                                                                                      |                                                                                    |                          |                                                                                                                          |
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|                               | xenograft models                        |                                      |                            | supports FOLFOX resistance; pathway disruption restores sensitivity.                                                                                                |                  | response testing.                                                                    |                                                                                    |                          | entary advanced CRC models.                                                                                              |
| [123] Bhavnani et al., 2016   | Review                                  | Wnt/stem cells                       | Contextual evidence only   | Wnt signalling in normal/malignant stem cells                                                                                                                       | Context only     | Not applicable for grading in this review                                            | Not independently appraised for grade                                              | Not independently graded | Secondary contextual source only.                                                                                        |
| [124] Herbst et al., 2014     | CRC cell transcriptomic study           | $\beta$ -catenin target-gene context | Graded supporting evidence | Defines $\beta$ -catenin target genes in CRC cells.                                                                                                                 | Partial/indirect | Transcriptomic/pathway characterisation.                                             | Cell models.                                                                       | Indirect                 | Foundational pathway evidence rather than acquired chemoresistance.                                                      |
| [125] Kongsavong et al., 2012 | CRC cell and human tumour pathway study | Wnt/ $\beta$ -catenin–YAP1 crosstalk | Graded supporting evidence | $\beta$ -catenin/TCF4 directly drives YAP1 gene expression in CRC cells, providing a mechanistic interface between Wnt/ $\beta$ -catenin and Hippo/YAP1 signalling. | Partial/indirect | $\beta$ -catenin knockdown and enhancer/transcriptional analyses of YAP1 regulation. | CRC cell models plus primary human colorectal tumour expression/localisation data. | Indirect                 | Establishes direct pathway crosstalk in CRC but does not demonstrate a drug-specific acquired-chemoresistance phenotype. |
| [126] Cammareri et al., 2025  | CRC experimental/translational study    | Multilineage plasticity              | Graded supporting evidence | Loss of colonic fidelity enables multilineage plasticity and metastatic progression.                                                                                | Partial/indirect | Functional lineage-state studies.                                                    | Advanced CRC models/human relevance.                                               | Indirect                 | Supports plasticity biology rather than a specific chemotherapy-resistance mechanism.                                    |

## Supplementary Table S1 and Supplementary Table S2

|                                 |                                 |                                                                                                                     |                                |                                                                                                                                                                |              |                                           |                                       |                          |                                                                                                                                                  |
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| [127]<br>Angius et al., 2021    | Review                          | CRC CSCs                                                                                                            | Contextual evidence only       | Molecular markers and pathways                                                                                                                                 | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Secondary contextual source only.                                                                                                                |
| [128]<br>Sphyrakis et al., 2021 | Review                          | Stem-cell niches                                                                                                    | Contextual evidence only       | Niche signalling in CRC                                                                                                                                        | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Secondary contextual source only.                                                                                                                |
| [129]<br>Sprangers et al., 2021 | Review                          | Organoids                                                                                                           | Contextual evidence only       | Organoid modelling of intestinal biology                                                                                                                       | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Secondary contextual source only.                                                                                                                |
| [130]<br>Swayden et al., 2020   | Review                          | 1. Introduction; 5.4. Therapy-Induced Signalling Adaptation, Cellular Plasticity and Drug-Tolerant Persister States | Contextual evidence only       | Used for contextual/background support in 1. Introduction; 5.4. Therapy-Induced Signalling Adaptation, Cellular Plasticity and Drug-Tolerant Persister States. | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [131]<br>Wang et al., 2023      | Review/contextual synthesis     | DTP/stable resistance and adaptive-state context                                                                    | Contextual evidence only       | Defines DTP biology and distinguishes reversible tolerance from stable resistance.                                                                             | Context only | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for conceptual context; did not independently increase a mechanistic or therapeutic evidence grade.                                         |
| [132]<br>Rehman et al., 2021    | Patient-derived CRC models with | Chemotherapy-induced DTP state                                                                                      | Graded mechanistic/therapeutic | CRC cells enter a reversible diapause-like DTP                                                                                                                 | Yes          | Longitudinal chemotherapy, withdrawal     | Patient-derived in vivo CRC models.   | Moderate                 | Direct DTP evidence with functional                                                                                                              |

## Supplementary Table S1 and Supplementary Table S2

|                                   | lineage/barcoding and in vivo treatment        |                                                | evidence                                | state that survives chemotherapy and can regrow after withdrawal.                           |                   | l and regrowth analysis.                                                |                                               |                          | l longitudinal validation in advanced patient-derived models; no prospective clinical validation. |
|-----------------------------------|------------------------------------------------|------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------------|-----------------------------------------------|--------------------------|---------------------------------------------------------------------------------------------------|
| [133] He et al., 2024             | Review                                         | DTP/plasticity and therapeutic vulnerabilities | Contextual evidence only                | Context for drug-tolerant states and strategies targeting them.                             | Context only      | Not applicable for grading in this review                               | Not independently appraised for grade         | Not independently graded | Used for contextual synthesis and did not independently increase an evidence grade.               |
| [134] Álvarez-Varela et al., 2022 | Patient-derived CRC organoids and mouse models | Chemotherapy-induced DTP/relapse               | Graded mechanistic/therapeutic evidence | MEX3A-positive persister cells survive chemotherapy and regenerate tumours after treatment. | Yes               | Lineage tracing, chemotherapy exposure and regeneration/relapse assays. | Patient-derived organoids and in vivo models. | Moderate                 | Direct DTP evidence across complementary advanced models.                                         |
| [135] Zhang et al., 2026          | CRC experimental study                         | KRAS/EGFR-targeted resistance                  | Graded supporting evidence              | Paneth-like lineage transition drives resistance to dual KRAS/EGFR targeting.               | Partial/in direct | Functional state/pathway manipulation.                                  | Advanced CRC models.                          | Indirect                 | Strong plasticity/resistance evidence in a targeted-therapy context.                              |
| [136] Bauzone et al., 2021        | 5-FU-sensitive and -resistant CRC cell models  | 5-FU/YAP-associated stemness                   | Graded mechanistic/therapeutic evidence | YAP-RAR/RXR crosstalk promotes stemness, self-renewal and 5-FU resistance.                  | Yes               | YAP/RAR-RXR perturbation with stemness and treatment-response assays.   | Cell models only.                             | Limited                  | Direct drug-specific functional evidence, but no complementary organoid/                          |

## Supplementary Table S1 and Supplementary Table S2

|                               |                                                                               |                                         |                                         |                                                                                                           |                   |                                                                                      |                                                                                                           |          | in vivo validation.                                                                                                  |
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| [137]<br>Jog et al., 2025     | CRC DTPs, patient-derived organoids and in vivo models                        | DTP metabolic resistance                | Graded mechanistic/therapeutic evidence | LPIN1-dependent lipid storage is a vulnerability of therapy-resistant/DTP CRC cells.                      | Yes               | LPIN1 inhibition/statins with ferroptosis and treatment-response assays.             | DTPs, PDOs and in vivo models.                                                                            | Moderate | Direct DTP mechanism and therapeutic vulnerability validated across complementary models.                            |
| [138]<br>Mzoughi et al., 2025 | WNT-dependent CRC models including patient-derived tumoroids and mouse models | FOLFIRI-associated oncofetal plasticity | Graded mechanistic/therapeutic evidence | YAP/AP-1-driven oncofetal reprogramming creates a drug-tolerant state associated with FOLFIRI resistance. | Yes               | State/pathway manipulation with chemotherapy-response testing.                       | Patient-derived tumoroids and mouse models.                                                               | Moderate | Direct chemotherapy-plasticity evidence across complementary advanced models.                                        |
| [139]<br>Alonso et al., 2026  | Patient-matched/experimental CRC study                                        | KRAS-inhibitor resistance               | Graded supporting evidence              | Concurrent genetic and non-genetic resistance mechanisms include adaptive state changes.                  | Partial/in direct | Longitudinal molecular/functional analysis.                                          | Human matched biopsies/experimental models.                                                               | Indirect | Resistance evidence is direct for KRAS inhibition, not conventional cytotoxic chemotherapy.                          |
| [140]<br>Ren et al., 2018     | CAF-CRC models, human CRC specimens and in vivo models                        | TME/exosomal chemoresistance            | Graded mechanistic/therapeutic evidence | CAF-derived exosomal H19 promotes stemness and chemoresistance through $\beta$ -catenin signalling.       | Yes               | Exosome/H19/miR-141 manipulation with chemosensitivity and tumour-initiation assays. | Human CRC specimens plus in vivo validation; human samples support pathway/stromal expression but are not | Moderate | Direct functional non-cell-autonomous mechanism reproduced in vivo; human tissue is supportive but does not directly |

## Supplementary Table S1 and Supplementary Table S2

|                                      |                                                        |                                 |                                         |                                                                                                                    |            |                                                             | treatment-response cohorts.                                                            |          | validate treatment resistance.                                                                                                                          |
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| [141] Gonçalves-Ribeiro et al., 2016 | CRC cells exposed to carcinoma-associated fibroblasts  | 5-FU/oxaliplatin TME resistance | Graded mechanistic/therapeutic evidence | CAFs alter CRC sensitivity to 5-FU and oxaliplatin.                                                                | Yes        | CAF-conditioned/co-culture treatment-response testing.      | Predominantly preclinical cellular evidence.                                           | Limited  | Direct TME-mediated chemotherapy evidence, but complementary mechanistic/in vivo validation is limited.                                                 |
| [142] Linares et al., 2023           | Human residual CRC tissue plus CAF experimental models | Platinum-treated TME resistance | Graded mechanistic/therapeutic evidence | Long-term platinum accumulation in CAFs activates pro-tumour stromal programmes and supports treatment resistance. | Yes        | Elemental imaging and CAF functional/mechanistic studies.   | Residual human CRC after platinum therapy with complementary experimental models.      | Strong   | Treatment-exposed human tissue directly supports the stromal phenomenon alongside mechanistic experimental evidence.                                    |
| [143] Wang et al., 2016              | CRC experimental models                                | IL-6/STAT3 platinum response    | Graded mechanistic/therapeutic evidence | IL-6/STAT3 signalling lowers sensitivity to platinum-containing therapy.                                           | Partial    | IL-6 inhibition with antitumour/treatment-response testing. | Preclinical evidence; carboplatin context is outside the principal CRC drugs reviewed. | Indirect | Supports cytokine-mediated platinum resistance conceptually, but the treatment context is not directly oxaliplatin/5-FU/irinotecan acquired resistance. |
| [144] Agorku et                      | CRC CAF/immune                                         | TME immune                      | Graded supporting                       | CAF NECTIN2 signalling                                                                                             | Partial/in | Functional immune-stromal                                   | CRC TME models.                                                                        | Indirect | Supports immunosuppressiv                                                                                                                               |

## Supplementary Table S1 and Supplementary Table S2

| al., 2024                | experimental study                                                  | suppression                         | evidence                                | suppressed effector T cells.                                                                               | direct | experiments.                                                                      |                                                                                                              |          | e TME biology, but not direct chemotherapy resistance.                                                                                                          |
|--------------------------|---------------------------------------------------------------------|-------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------|--------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [145] Tang et al., 2018  | CRC cells, CAF/hypoxia models, PDXs and patient outcome data        | Hypoxic TME chemoresistance         | Graded mechanistic/therapeutic evidence | HIF-1 $\alpha$ /TGF- $\beta$ 2-GLI2 signalling drives stemness and chemotherapy resistance in hypoxic CRC. | Yes    | Genetic/pharmacological pathway inhibition reverses TME-mediated chemoresistance. | Patient relapse association and chemotherapy-responsive/resistant PDX models.                                | Strong   | Concordant functional mechanism, patient outcome association and patient-derived in vivo validation.                                                            |
| [146] Xu et al., 2019    | CRC cells, human CRC specimens and xenografts                       | Hypoxia-induced drug resistance     | Graded mechanistic/therapeutic evidence | HIF-1 $\alpha$ /miR-338-5p/IL-6 feedback drives hypoxia-mediated resistance.                               | Yes    | miRNA/pathway perturbation and chemosensitivity assays.                           | Human CRC specimens show pathway correlations; xenografts provide direct oxaliplatin-sensitivity validation. | Moderate | Direct functional mechanism with complementary in vivo validation; human tissue supports pathway relevance but does not directly validate treatment resistance. |
| [147] Lotti et al., 2013 | Matched human CRC specimens, CAF/CIC models and in vivo experiments | Chemotherapy-induced TME remodeling | Graded mechanistic/therapeutic evidence | Chemotherapy activates CAFs to maintain CRC-initiating cells via IL-17A.                                   | Yes    | CAF/IL-17A manipulation with self-renewal and tumour-growth assays.               | Matched patient samples before/after cytotoxic treatment plus in vivo models.                                | Strong   | Direct treatment-induced stromal mechanism with human treatment-exposed and in vivo validation.                                                                 |

## Supplementary Table S1 and Supplementary Table S2

|                             |                                                                            |                                             |                                         |                                                                                                                                     |                  |                                                                                             |                                                                     |          |                                                                                                                                                                  |
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| [148]<br>Yin et al., 2025   | CAF-CRC models, neoadjuvant-treated patient CAFs and in vivo models        | Chemotherapy-induced CAF/DKK1 resistance    | Graded mechanistic/therapeutic evidence | Chemotherapy induces CAF-derived DKK1, promoting immunosuppression and chemoresistance; DKK1 neutralisation improves 5-FU response. | Yes              | p53/MEK-ERK/DKK1 perturbation and DKK1 neutralisation with chemotherapy.                    | Neoadjuvant-treated patient CAFs plus in vivo validation.           | Moderate | Direct functional mechanism with treatment-exposed human stromal support and in vivo validation; the DKK1-neutralising therapeutic strategy remains preclinical. |
| [149]<br>Calon et al., 2012 | CRC stromal experimental/translational study                               | TGF- $\beta$ stromal programme              | Graded supporting evidence              | TGF- $\beta$ -driven stromal programmes support metastatic fitness.                                                                 | Partial/indirect | Stromal pathway manipulation.                                                               | Human/preclinical CRC models.                                       | Indirect | Relevant non-cell-autonomous biology, but not a direct chemotherapy-resistance mechanism.                                                                        |
| [150]<br>Hu et al., 2015    | CRC cell/CSC models, patient-derived xenograft material and in vivo models | Fibroblast-exosome-mediated chemoresistance | Graded mechanistic/therapeutic evidence | Fibroblast-derived exosomes prime CRC stem-like cells and increase 5-FU/oxalipatin resistance.                                      | Yes              | Exosome-transfer/depletion experiments with chemotherapy-response and tumour-growth assays. | Patient-derived xenograft CSCs and in vivo chemotherapeutic models. | Moderate | Direct functional non-cell-autonomous mechanism validated across complementary patient-derived and in vivo models; no direct clinical validation.                |

## Supplementary Table S1 and Supplementary Table S2

|                            |                                                                               |                                                       |                                         |                                                                                           |              |                                                                                         |                                                                                                        |                          |                                                                                                                                                          |
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| [151]<br>Deng et al., 2020 | CAF-exosome/<br>CRC cell and in vivo models with human tumour-stroma analysis | Oxaliplatin resistance                                | Graded mechanistic/therapeutic evidence | CAF-derived exosomal CCAL activates $\beta$ -catenin and promotes oxaliplatin resistance. | Yes          | CCAL/exosome perturbation with apoptosis, $\beta$ -catenin and chemosensitivity assays. | Human CRC stromal expression plus in vivo validation; human tissue is not a treatment-response cohort. | Moderate                 | Direct functional mechanism reproduced in vivo; human tumour-stroma expression supports relevance but does not directly validate oxaliplatin resistance. |
| [152]<br>Ning et al., 2021 | CRC patient serum, resistant cells and mouse xenografts                       | Oxaliplatin/FOLFOTX resistance and immune suppression | Graded mechanistic/therapeutic evidence | Tumour exosomal miR-208b promotes Treg expansion and oxaliplatin resistance.              | Yes          | Exosome/miR-208b-PDCD4 manipulation and Treg/treatment-response assays.                 | FOLFOTX-treated patient serum plus in vivo xenograft validation.                                       | Strong                   | Direct functional mechanism with human treatment-response biomarker and in vivo validation.                                                              |
| [153]<br>Lee et al., 2020  | Human translational study                                                     | CRC immune landscape                                  | Contextual evidence only                | Lineage-dependent immune organisation                                                     | Context only | Not applicable for grading in this review                                               | Not independently appraised for grade                                                                  | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade.         |

## Supplementary Table S1 and Supplementary Table S2

|                             |                                                                         |                                                     |                                         |                                                                                                                                                                                                                                            |              |                                                                                                                   |                                                                                                                           |                          |                                                                                                                                                  |
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| [154]<br>Pelka et al., 2021 | Human spatial study                                                     | CRC TME                                             | Contextual evidence only                | Spatial immune organisation                                                                                                                                                                                                                | Context only | Not applicable for grading in this review                                                                         | Not independently appraised for grade                                                                                     | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [155]<br>Wu et al., 2022    | Human CRC liver-metastasis single-cell and spatial transcriptomic study | Neoadjuvant chemotherapy-associated TME remodelling | Graded mechanistic/therapeutic evidence | Neoadjuvant chemotherapy is associated with substantial remodelling of the immune microenvironment in colorectal liver metastases, including macrophage-state changes and restoration of antitumour immune balance in responsive patients. | Yes          | Single-cell RNA-seq and spatial transcriptomic profiling; no perturbational validation of the inferred mechanism. | Matched human colorectal liver-metastasis samples, including chemotherapy-treated responsive and non-responsive patients. | Limited                  | Direct human treatment - associated evidence, but the study is observational and does not establish causal functional resistance mechanisms.     |
| [156]<br>Qin et al., 2023   | Human rectal cancer single-cell/spatial study                           | Neoadjuvant chemotherapy and CAF remodelling        | Graded mechanistic/therapeutic evidence | Neoadjuvant chemotherapy reshapes CAF states and                                                                                                                                                                                           | Yes          | Single-cell/spatial observational analysis.                                                                       | Human paired/treatment-exposed tissue.                                                                                    | Limited                  | Direct human treatment - associated evidence,                                                                                                    |

## Supplementary Table S1 and Supplementary Table S2

|                            |                                                         |                                    |                                         |                                                                                                                            |              |                                                                             |                                                                                                         |                   |                                                                                                                                |
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|                            |                                                         |                                    |                                         | tumour-microenvironment interactions.                                                                                      |              |                                                                             |                                                                                                         |                   | but mechanistic causality is not established.                                                                                  |
| [157] Tie et al., 2016     | Prospective/longitudinal clinical colon cancer cohort   | Minimal residual disease biomarker | Graded mechanistic/therapeutic evidence | Post-treatment ctDNA detects residual disease and predicts recurrence.                                                     | Yes          | Longitudinal clinical biomarker assessment.                                 | Human clinical cohort.                                                                                  | Limited           | Strong clinical association for residual disease, but this is a biomarker rather than a functional resistance-mechanism study. |
| [158] Schøler et al., 2017 | Longitudinal clinical CRC cohort                        | ctDNA monitoring                   | Graded mechanistic/therapeutic evidence | Serial ctDNA can detect recurrent/evolving CRC after treatment.                                                            | Yes          | Longitudinal clinical monitoring.                                           | Human clinical cohort.                                                                                  | Limited           | Clinically relevant longitudinal evidence without functional validation of a resistance mechanism.                             |
| [159] Avolio et al., 2026  | Metastatic CRC patient-derived xenografts and tumoroids | FOLFIRI resistance                 | Graded mechanistic/therapeutic evidence | FOLFIRI-resistant mCRC models show distinct molecular/functional resistance states and targetable DNA-repair dependencies. | Yes          | Functional resistance profiling and intervention in patient-derived models. | PDXs and patient-derived tumors; translationally human-derived but not prospective clinical validation. | Moderate          | Direct FOLFIRI-resistance evidence across complementary patient-derived models.                                                |
| [160] Guinney et           | Molecular-classification study                          | CMS                                | Contextual evidence only                | Consensus molecular subtypes                                                                                               | Context only | Not applicable for grading in                                               | Not independently appraised                                                                             | Not independently | Used for clinical, biological,                                                                                                 |

## Supplementary Table S1 and Supplementary Table S2

|                               |                                                                           |                                |                                            |                                                                           |                     |                                                           |                                                            |                             |                                                                                                                                                        |
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| al., 2015                     |                                                                           |                                |                                            |                                                                           |                     | this review                                               | ed for grade                                               | grad ed                     | methodol ogical or backgrou nd context; did not independ ently increase a mechanis tic or therapeut ic evidence grade.                                 |
| [161] Ten Hoor n et al., 2022 | Systemati c review/meta-analysis                                          | CMS                            | Context ual evidenc e only                 | Clinical value of CRC molecular subtypes                                  | Cont ext only       | Not applicable for grading in this review                 | Not indepen dently apprais ed for grade                    | Not inde pend ently grad ed | Used for clinical, biological , methodol ogical or backgrou nd context; did not independ ently increase a mechanis tic or therapeut ic evidence grade. |
| [162] Arqué s et al., 2016    | CRC targeted-therapy resistanc e study                                    | PI3K/AK T inhibitor resistance | Graded supporti ng evidenc e               | Tankyras e/Wnt inhibition reverses resistance to PI3K/AK T inhibitors.    | Parti al/in direc t | Pathway inhibition and resistance assays.                 | Prelini cal CRC models.                                    | Indir ect                   | Direct resistance biology in a targeted-therapy rather than cytotoxic-chemothe rapy context.                                                           |
| [163] Song et al., 2018       | Acquired 5-FU-resistant CRC cells, mouse models and chemothe rapy-treated | 5-FU/YAP resistance            | Graded mechanis tic/ther apeutic evidenc e | YAP signalling is functiona lly required for acquired 5-FU resistance and | Yes                 | YAP knockdow n with 5-FU sensitisati on in vitro/in vivo. | Human chemot herapy-treated cohort plus mouse validati on. | Stron g                     | Direct acquired-resistance mechanis m with concordant functiona l, in vivo and human                                                                   |

## Supplementary Table S1 and Supplementary Table S2

|                             | patient cohort                  |                         |                            | relates to relapse after 5-FU-based chemotherapy.              |                   |                                           |                                       |                          | treatment-outcome evidence.                                                                                                                      |
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| [164] Sakshaug et al., 2023 | Systematic review               | PDOs                    | Contextual evidence only   | Predictive value of organoids                                  | Context only      | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [165] Clara et al., 2020    | Review                          | CSC pathways            | Contextual evidence only   | Clinical targeting of CSC-associated pathways                  | Context only      | Not applicable for grading in this review | Not independently appraised for grade | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade. |
| [166] Lu et al., 2024       | CRC in vivo drug-delivery study | Notch-targeted strategy | Graded supporting evidence | Tumour-responsive Notch1 shRNA delivery suppresses CRC growth. | Partial/in direct | Functional Notch1 attenuation.            | In vivo CRC models.                   | Indirect                 | Therapeutic proof-of-concept without direct acquired chemotherapy-resistance modelling.                                                          |

## Supplementary Table S1 and Supplementary Table S2

|                                |                                                               |                                          |                                         |                                                                                                            |                   |                                                                                             |                                                           |                          |                                                                                            |
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| [167]<br>Yap et al., 2025      | Phase 1/2 solid-tumour trial                                  | YAP/TEAD druggability                    | Graded supporting evidence              | VT3989 demonstrates clinical YAP/TEAD pathway inhibition in solid tumours.                                 | Partial/in direct | Clinical pharmacological intervention.                                                      | Human trial, not resistance-selected CRC.                 | Indirect                 | Clinical pathway-targeting evidence, but not CRC chemotherapy-resistance validation.       |
| [168]<br>Lombardo et al., 2011 | CRC CSC and mouse study                                       | Differentiation-based chemosensitisation | Graded supporting evidence              | BMP4 differentiation increases CRC stem-cell response to chemotherapy.                                     | Partial/in direct | BMP4 differentiation with chemotherapy-response testing.                                    | In vivo mouse validation.                                 | Indirect                 | Functional chemosensitisation evidence, but not an acquired-resistance model.              |
| [169]<br>Gao et al., 2025      | Human NAC single-cell data, CRC cell models and animal models | Oxaliplatin/neoadjuvant chemoresistance  | Graded mechanistic/therapeutic evidence | KLF5-PI3K/AKT signalling drives neoadjuvant oxaliplatin resistance and is targetable with PI3K inhibition. | Yes               | Mechanistic KLF5/PI3K-AKT perturbation, drug screening and oxaliplatin combination testing. | Treatment-exposed human scRNA-seq plus animal validation. | Strong                   | Direct human treatment-state evidence with concordant mechanistic and in vivo validation.  |
| [170]<br>Herpers et al., 2022  | Patient-derived organoid and in vivo study                    | EGFR×LGR5 targeted strategy              | Graded supporting evidence              | PDO screening identified petosemta mab/MCLA-158 as a tumour-selective therapeutic strategy.                | Partial/in direct | Functional PDO screening and in vivo testing.                                               | PDO and in vivo models.                                   | Indirect                 | Strong therapeutic proof-of-concept, but not acquired cytotoxic chemoresistance.           |
| [171]<br>Barai et al., 2021    | Review                                                        | MSS CRC immunotherapy                    | Contextual evidence only                | Combination immunotherapy strategies                                                                       | Context only      | Not applicable for grading in this review                                                   | Not independently appraised for grade                     | Not independently graded | Used for clinical, biological, methodological or background context; did not independently |

## Supplementary Table S1 and Supplementary Table S2

|                               |                                                        |                                      |                          |                                                                      |              |                                           |                                           |                          |                                                                                                                                                                                  |
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|                               |                                                        |                                      |                          |                                                                      |              |                                           |                                           |                          | increase a mechanistic or therapeutic evidence grade.                                                                                                                            |
| [172] Hamid et al., 2024      | Review                                                 | MSS metastatic CRC                   | Contextual evidence only | Immunotherapy context                                                | Context only | Not applicable for grading in this review | Not independently appraised for grade     | Not independently graded | Used for clinical, biological, methodological or background context; did not independently increase a mechanistic or therapeutic evidence grade.                                 |
| [173] Shah et al., 2023       | Randomised clinical trial                              | Mechanism-guided combination therapy | Contextual evidence only | Clinical outcome of napabucasin plus FOLFIRI-based treatment.        | Context only | Randomised clinical treatment comparison  | Human phase III trial                     | Not independently graded | Used to demonstrate that adding a putative resistance-targeting agent does not necessarily improve clinical outcome; not used to grade a specific acquired-resistance mechanism. |
| [174] Antonietti et al., 2024 | Randomised phase II clinical trial, four-year analysis | FOLFOXIRI/bevacizumab ± atezolizumab | Contextual evidence only | Updated overall-survival and exploratory biomarker outcomes from the | Context only | Randomised clinical treatment comparison  | Human phase II trial; four-year follow-up | Not independently graded | Used for clinical treatment-selection context rather than to grade a specific acquired-                                                                                          |

## Supplementary Table S1 and Supplementary Table S2

|                                         |                                                                                                     |                                                                                   |                                                           |                                                                                                                                                                         |                     |                                                                                                                             |                                                                                                                                                |                                            |                                                                                                                                                                                                            |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                         |                                                                                                     |                                                                                   |                                                           | AtezoTRI<br>BE trial.                                                                                                                                                   |                     |                                                                                                                             |                                                                                                                                                |                                            | resistance<br>mechanis<br>m; overall<br>survival<br>was not<br>the<br>primary<br>endpoint.                                                                                                                 |
| [175]<br>Wen<br>et al.,<br>2023         | Review                                                                                              | Single-<br>cell<br>sequenci<br>ng                                                 | Context<br>ual<br>evidenc<br>e only                       | Single-cell<br>profiling<br>in CRC                                                                                                                                      | Cont<br>ext<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review                                                                    | Not<br>independ<br>ently<br>apprais<br>ed for<br>grade                                                                                         | Not<br>inde<br>pend<br>ently<br>grad<br>ed | Used for<br>methodol<br>ogical<br>context.                                                                                                                                                                 |
| [176]<br>Alza<br>mami,<br>2023          | Review                                                                                              | Single-<br>cell TME                                                               | Context<br>ual<br>evidenc<br>e only                       | Immune-<br>landscape<br>implicatio<br>ns                                                                                                                                | Cont<br>ext<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review                                                                    | Not<br>independ<br>ently<br>apprais<br>ed for<br>grade                                                                                         | Not<br>inde<br>pend<br>ently<br>grad<br>ed | Used for<br>methodol<br>ogical/co<br>ntextual<br>synthesis.                                                                                                                                                |
| [177]<br>Joanit<br>o et<br>al.,<br>2022 | Human<br>CRC<br>single-<br>cell and<br>bulk<br>transcript<br>omic<br>study                          | CRC<br>epithelial<br>heteroge<br>neity and<br>molecula<br>r<br>classificat<br>ion | Context<br>ual<br>evidenc<br>e only                       | Single-cell<br>profiling<br>identifies<br>intrinsic<br>epithelial<br>tumour<br>states and<br>refines<br>bulk<br>consensus<br>molecular<br>classificati<br>on in<br>CRC. | Cont<br>ext<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review                                                                    | Large<br>multi-<br>cohort<br>human<br>CRC<br>single-<br>cell<br>dataset<br>with<br>validati<br>on in<br>bulk<br>transcri<br>ptomic<br>cohorts. | Not<br>inde<br>pend<br>ently<br>grad<br>ed | Used to<br>support<br>molecular<br>-<br>classificat<br>ion and<br>tumour-<br>heterogen<br>eity<br>context<br>rather<br>than a<br>specific<br>acquired<br>chemothe<br>rapy-<br>resistance<br>mechanis<br>m. |
| [178]<br>Chen<br>et al.,<br>2026        | Single-<br>cell<br>bioinforma<br>tic<br>CRC<br>resistanc<br>e study<br>with<br>external<br>datasets | Oxaliplati<br>n-<br>resistant<br>subpopul<br>ations                               | Graded<br>mechani<br>stic/ther<br>apeutic<br>evidenc<br>e | An EpC2<br>epithelial<br>state is<br>associated<br>with<br>oxaliplati<br>n<br>resistance<br>and<br>suggests<br>candidate<br>therapies.                                  | Yes                 | Computati<br>onal<br>identificati<br>on and<br>external<br>dataset<br>validation;<br>no direct<br>drug<br>perturbati<br>on. | Single-<br>cell and<br>resistan<br>t-cell-<br>line<br>datasets<br>.                                                                            | Limi<br>ted                                | Direct<br>resistance<br>profiling,<br>but<br>functiona<br>l causal<br>validatio<br>n of the<br>proposed<br>state/ther<br>apy is<br>absent.                                                                 |
| [179]<br>Nojim<br>a et<br>al.,<br>2025  | Patient-<br>derived<br>colorectal<br>organoid<br>s with<br>scRNA-                                   | DTP<br>identifica<br>tion/targe<br>ting                                           | Graded<br>mechani<br>stic/ther<br>apeutic<br>evidenc<br>e | Machine-<br>learning-<br>defined<br>DTP<br>populatio<br>ns can be                                                                                                       | Yes                 | Organoid<br>viability<br>testing of<br>predicted<br>candidate<br>drugs.                                                     | Patient-<br>derived<br>organoi<br>d<br>model;<br>no in                                                                                         | Limi<br>ted                                | Functiona<br>l patient-<br>derived<br>evidence,<br>but<br>validatio                                                                                                                                        |

## Supplementary Table S1 and Supplementary Table S2

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|                                          | seq,<br>machine<br>learning<br>and drug<br>testing                            |                                                                                                   |                                     | targeted<br>by<br>candidate<br>drug<br>combinati<br>ons in<br>malignant<br>organoids<br>.                                                                                                            |                     |                                                          | vivo/cli<br>nical<br>validati<br>on.                                                                                                                   |                                            | n remains<br>within a<br>single<br>model<br>class.                                                                                                                                                          |
| [180]<br>Carra<br>nza et<br>al.,<br>2024 | Review                                                                        | Spatial<br>biology                                                                                | Context<br>ual<br>evidenc<br>e only | Spatial<br>profiling<br>in CRC                                                                                                                                                                       | Cont<br>ext<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review | Not<br>independ<br>ently<br>apprais<br>ed for<br>grade                                                                                                 | Not<br>inde<br>pend<br>ently<br>grad<br>ed | Methodol<br>ogical/co<br>ntextual<br>source<br>only.                                                                                                                                                        |
| [181]<br>Guo<br>et al.,<br>2024          | Review                                                                        | Spatial<br>transcript<br>omics                                                                    | Context<br>ual<br>evidenc<br>e only | Spatiotem<br>poral<br>profiling<br>context                                                                                                                                                           | Cont<br>ext<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review | Not<br>independ<br>ently<br>apprais<br>ed for<br>grade                                                                                                 | Not<br>inde<br>pend<br>ently<br>grad<br>ed | Methodol<br>ogical/co<br>ntextual<br>source<br>only.                                                                                                                                                        |
| [182]<br>Xiao<br>et al.,<br>2024         | Human<br>CRC<br>single-<br>cell and<br>spatial<br>transcript<br>omic<br>study | Spatial<br>tumour<br>heteroge<br>neity and<br>tumour-<br>microenv<br>ironment<br>interactio<br>ns | Context<br>ual<br>evidenc<br>e only | Integrated<br>single-cell<br>and<br>spatial<br>transcript<br>omics<br>maps<br>malignant<br>-cell<br>heterogen<br>eity and<br>spatial<br>tumour-<br>stromal/i<br>mmune<br>interactio<br>ns in<br>CRC. | Cont<br>ext<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review | Human<br>CRC<br>tumour-<br>normal-<br>blood<br>samples<br>profiled<br>by<br>scRNA-<br>seq<br>with<br>spatial<br>transcri<br>ptomic<br>integrat<br>ion. | Not<br>inde<br>pend<br>ently<br>grad<br>ed | Directly<br>demonstr<br>ates<br>integrate<br>d spatial<br>and<br>single-cell<br>profiling<br>in CRC,<br>but does<br>not test a<br>specific<br>acquired<br>chemothe<br>rapy-<br>resistance<br>mechanis<br>m. |
| [183]<br>Gupta<br>et al.,<br>2019        | Review                                                                        | Colon<br>CSCs                                                                                     | Context<br>ual<br>evidenc<br>e only | CSC<br>therapeuti<br>c<br>targeting                                                                                                                                                                  | Cont<br>ext<br>only | Not<br>applicable<br>for<br>grading in<br>this<br>review | Not<br>independ<br>ently<br>apprais<br>ed for<br>grade                                                                                                 | Not<br>inde<br>pend<br>ently<br>grad<br>ed | Secondar<br>y<br>contextua<br>l source<br>only.                                                                                                                                                             |