

POSITIONING OF **MDM2** AS AN ONCOLOGY DRUG TARGET

ASSESSMENT

SCORE

Successful target-like properties

16/25

The proprietary AI model was trained to differentiate successful drug targets from those that failed clinical trials
MDM2 is frequently amplified and the levels of these amplifications strongly suggest that MDM2 play a critical role in tumors where it is amplified.

Translatability of pre-clinical models

11/25

The technology evaluates whether dependencies observed in cell lines are present in real patient tumor data
MDM2 and p53 dependency as well as functional compensation with MDM4 observed in cell line models is very strong in patient data. Multiple other dependencies were observed that might affect the patient selection strategy.

Clinical response rates in the primary indication

8/25

The AI model measures how critical for the tumor is the activity of drug target
Two ubiquitous resistance mechanism will likely limit the clinical response rates. The experimental design testing the impact of these resistance mechanism on MDM2i response rate is provided.

Market expansion and competitive advantage over other drugs

12/25

The AI model compares MDM2 with other drug targets in possible indications
Sarcoma is by far the best indication. However, response rates will be limited by potential resistance mechanisms, even in MDM2i naive patients. Other dependencies should be used to maximise the clinical response rates.

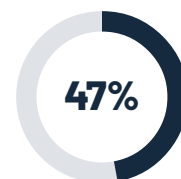
CONCLUSIONS & RECOMMENDATIONS

Sarcoma offers the strongest opportunity for clinical success of MDM2i.

However, if identified resistance mechanisms are validated, the clinical response rates will be low.

Yet, detected dependencies beyond p53 open an opportunity for a large cohort expansion.

PROBABILITY
OF SUCCESS



ANALYSIS OF MDM2 POTENTIAL AS A DRUG TARGET

SUMMARY

MDM2 is being evaluated as a therapeutic target in multiple clinical trials, and despite promising preclinical efficacy, its clinical effectiveness has yet to be conclusively demonstrated.

Using Gordion technology, the MDM2 potential as a drug target was assessed. Several key observations informing the decision whether to continue/kill the MDM2 program were made:

1. MDM2 exhibits the characteristics of a highly effective therapeutic target.
2. The dependency between MDM2 and TP53 status observed in cell line models is very strong in patient data.
3. Strong and ubiquitous resistance mechanisms to MDM2 inhibition have been identified, which, despite MDM2's high potential as a drug target, significantly reduce its chances for clinical success.
4. Yet, other dependencies beyond TP53 were observed in patient data, suggesting that MDM2i could succeed in the clinic if a patient stratification beyond TP53 status is used.
5. Preliminary results demonstrated that "dependencies beyond TP53" could be used to design synergistic drug combinations, further improving the clinical response rates.

CONCLUSION & RECOMMENDATION

Patient data indicate that MDM2 is a highly promising drug target in significant patient cohorts; however, the presence of ubiquitous resistance mechanisms reduces the likelihood of its clinical success. Yet, correct patient stratification strategy and drug combinations could increase the probability of success of MDM2i programs.

INTRODUCTION TO THE TECHNOLOGY

The concept of gene essentiality measurement in real-patient data

The Gordion Platform was designed to identify genes essential for cancer survival. The products of such genes constitute the best drug targets, which inhibition results in high clinical response rates.

Gene losses can lead to faster growth of a tumor cell, and such losses accumulate during tumor evolution (the best examples are tumor suppressor genes like p53 or PTEN). On the other hand, the loss of a gene essential for cancer survival leads to reduced fitness; therefore, such gene losses are eliminated during tumor evolution. Genes essential for tumor survival are frequently activated or amplified. Gordion's technology detects patterns of loss, activation, and amplification of any given gene and translates them into the probability of success for any drug target.

On the DNA level, the function of a gene can be lost in multiple ways, for example:

- the presence of a protein-altering single-nucleotide variant (SNV) or a short indel,
- by structural variants (SVs), affecting the gene sequence, promoters, or enhancers,
- by eliminating the entire copy of the gene by deletion.

Very few genes are lost completely (loss of all functional copies, bi-allelic loss) in sufficient numbers in tumors to facilitate robust statistical analysis. However, Gordion discovered that analysis of losses of a single gene copy (mono-allelic loss) directly in patient data, combined with the analysis of gene activations and amplifications, reveals the relevance of a gene for tumor survival.

Two different databases will be used for the analysis.

- 2,607 Whole-Genome Sequencing Datasets – a collection of sequences of whole cancer genomes and matched normal genomes from the same patient from breast, liver, lung, ovarian, and pancreatic cancers, with fully characterized genetic mutation profiles including single-nucleotide variants, in-dels, copy number alterations, and structural changes. The majority of the analyzed samples originated from refractory, metastatic tumors.
- 9,966 Copy Number Alterations Datasets combined with Whole-Exome Sequencing (CNA+WES). Samples originated from primary tumors.

Detailed information regarding databases is presented in the supplementary.

MDM2 AS A DRUG TARGET

MDM2 Proto-Oncogene

HGNC: [6973](#)

NCBI Gene: [4193](#)

Ensembl: [ENSG00000135679](#)

OMIM®: [164785](#)

UniProtKB/Swiss-Prot: [Q00987](#)

MDM2 is an oncogenic protein that functions as a key negative regulator of the tumor suppressor p53 (encoded by the TP53 gene). It acts mainly as an E3 ubiquitin ligase, promoting ubiquitination and subsequent proteasomal degradation of p53, thus controlling p53 levels and activity (1). By binding to the transactivation domain of p53, MDM2 inhibits p53's ability to activate transcription of target genes involved in cell cycle arrest and apoptosis (2,3). This regulation forms a feedback loop where p53 induces MDM2 expression, which in turn downregulates p53. MDM2 overexpression or amplification is frequently observed in various human cancers and contributes to tumor development by inactivating p53-mediated tumor suppression.

MDM2 IS NOT ACCUMULATING POINT MUTATIONS

The cancer genome is burdened with a high number of mutations. However, their distribution is not random. Genes under positive selection pressure (oncogenes and tumor suppressors) tend to accumulate more point mutations than others, while those under negative selective pressure (essential genes) accumulate fewer. To analyze the accumulation of protein-altering mutations at chromosome 12, we used the Gene Mutational Load (GML) analysis.

The GML for a gene is calculated by counting protein-altering mutations (SNVs and indels) in each genome. The number of mutations is normalized by the mutational burden for the individual tumor (total mutations in that tumor's genome) to compensate for differences in mutation rates between the tumors, and by the length of the gene's coding sequence (5).

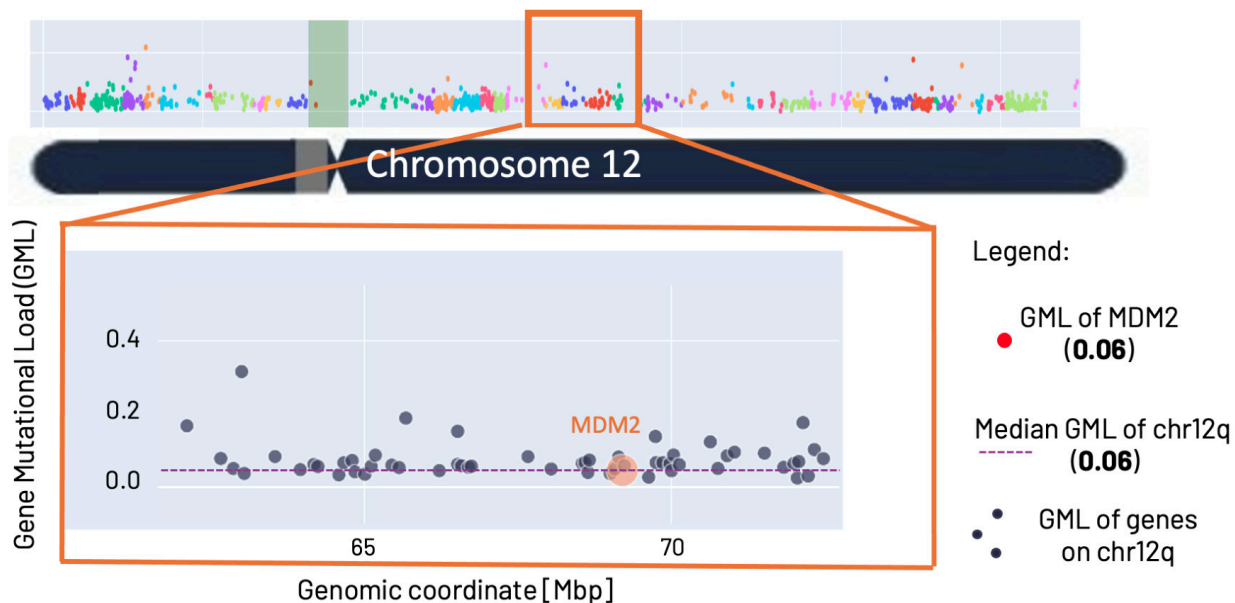


Fig. 1. Analysis of Gene Mutational Load (GML), showing the burden of point mutations in genes on the q arm of chromosome 12. Each dot represents a distinct protein-coding gene, and the horizontal line is the median for all genes.

GML analysis (Fig. 1) showed that MDM2 accumulates protein-altering mutations at a median rate of 0.06, which matches the average mutation rate of genes located on the q arm of chromosome 12. This result is consistent with MDM2 being a potentially good drug target.

THE BI-ALLELIC LOSS OF MDM2 WAS NOT OBSERVED.

Both copies of a gene (bi-allelic loss) can be inactivated by two point mutations, two deletions, or a combination of one deletion and one point mutation. In both patient datasets (altogether 12,573 patient samples), we did not observe a single case of bi-allelic MDM2 loss. Mono-allelic loss of MDM2, where one gene copy is deleted but one functional copy remains, is also rare, supporting the importance of MDM2 for tumor survival. Strong evolutionary pressure to preserve functional gene copy is typical for essential genes, but it also suggests that MDM2 is a good therapeutic target.

MDM2 IS OFTEN AMPLIFIED

Genes essential for tumor survival are frequently amplified. MDM2 amplifications were observed in over 5% of tumors pan-cancer, which is considerably higher than the median amplification rate for all genes (1.1%). This is consistent with the literature data (6,7,8). In certain tumor types, such as adrenal, bladder, lung, and testicular cancers, the frequency of MDM2 amplification approaches 10%. Sarcomas are a notable outlier, with amplification levels reaching up to 20% (Fig.2).

Good drug targets like HER2 often acquire multiple additional copies of the gene, which significantly increase the gene expression (9). We analyzed each sample in terms of the level of amplification and categorized amplification as high (more than 6 extra copies) and low (2 - 6 extra copies) (Fig. 2). Sarcoma not only displayed

the highest % of samples amplified, but 100% of these samples had more than 6 additional copies of MDM2. This is unprecedented and identifies sarcoma as an outlier tissue that should be prioritized for drug development efforts.

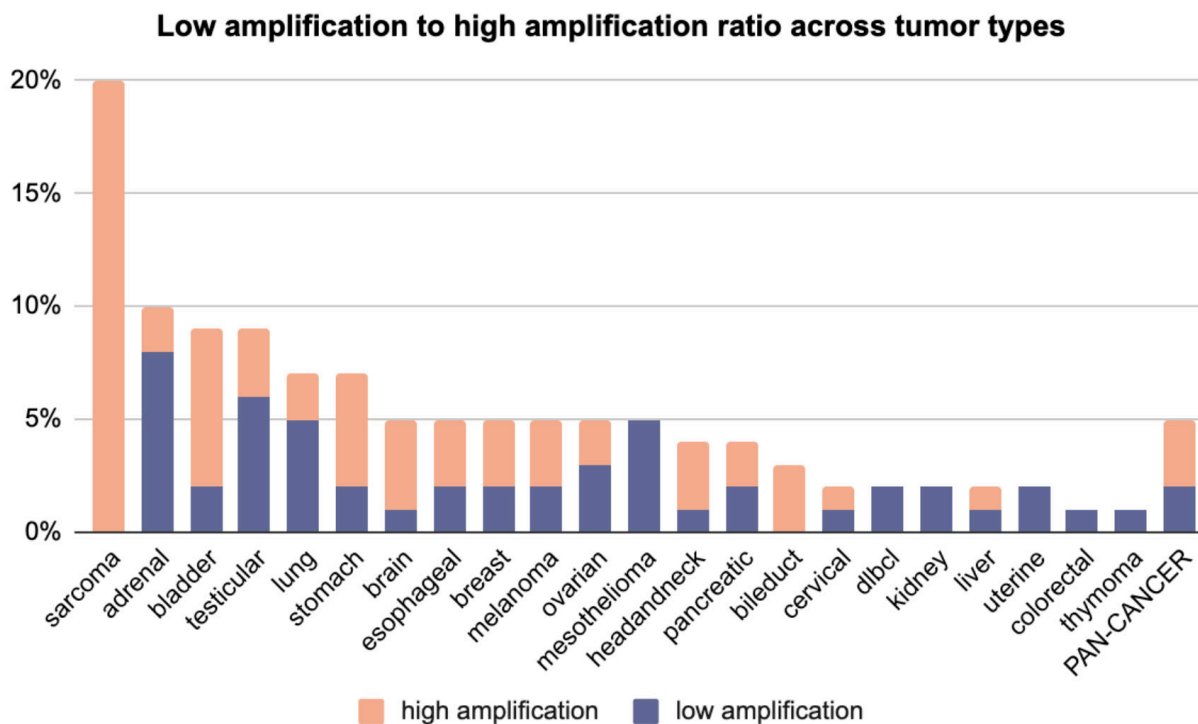


Fig. 2. Level of MDM2 amplifications across tumor types. Bar colors represent the ratio of high amplifications to low amplifications. High amplifications (more than 6 extra copies) are marked in orange, and low amplifications (2-6 extra copies) are marked in blue.

The analysis showed that in sarcomas, high amplifications comprised 100% of all amplifications detected. A high proportion of high amplifications was also observed in bladder, stomach, and brain tumors, although the overall frequency of amplification in these tumors was significantly lower than in sarcomas (<10%). This highlights MDM2 potential as an effective target for oncological therapies.

ESSENTIALITY OF MDM2 IN DIFFERENT TUMOR TYPES

To design clinical strategy for MDM2i, Gordion performed an unbiased analysis of MDM2 potential as a drug target. We asked whether there are any tissues with a lower occurrence of alterations downregulating MDM2. Gordion is using all alterations leading to gene downregulation (alterations including SNV, Indels, SV, and deletions, and mono-allelic gene loss) to identify tissues, where the reduction of MDM2 activity will lead to cell death. The rationale: if MDM2 accumulates fewer mutations downregulating MDM2 than in other tissues, it might suggest the increased essentiality of MDM2.

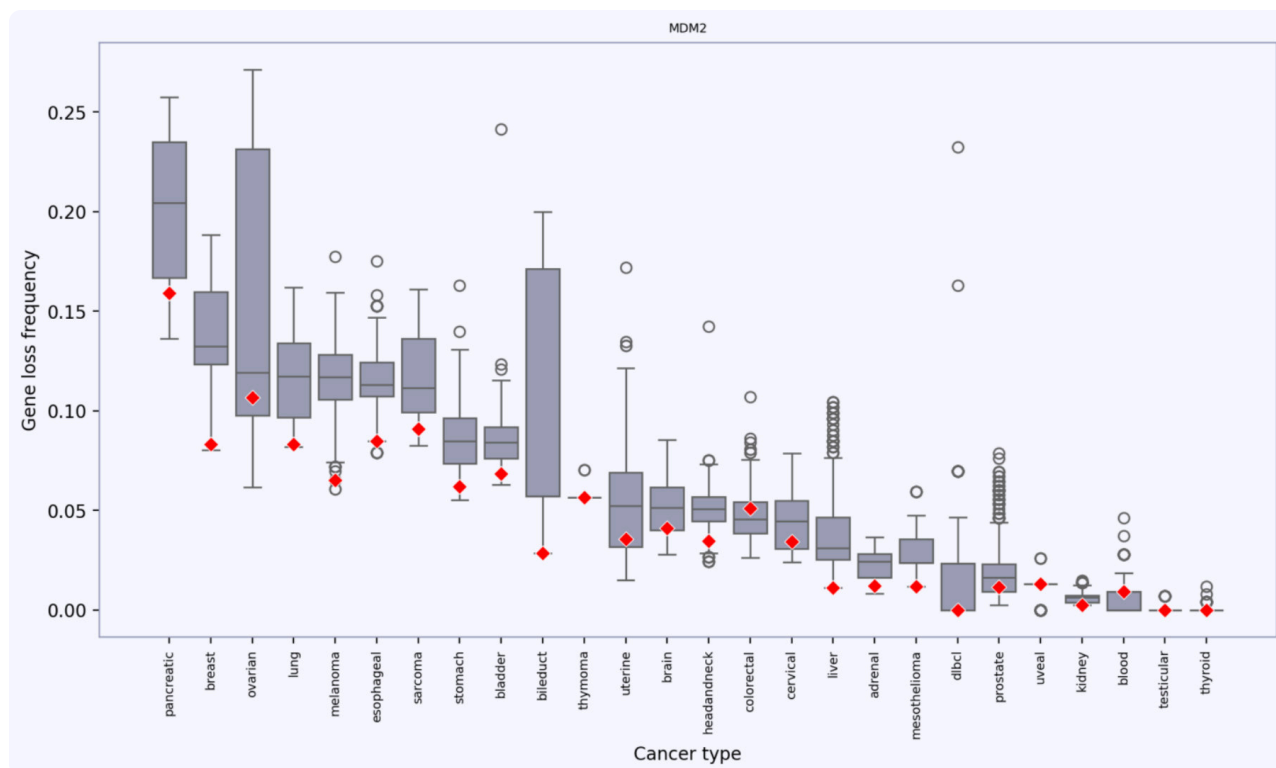


Figure 3. The importance of MDM2 in different tumors is illustrated by the difference between the median gene loss across the chromosome arm (the horizontal line on the bar plots) and MDM2 gene loss represented by a red diamond

In most tumor types, the MDM2 gene is lost significantly less frequently than the genomic average, suggesting a selective advantage in retaining fully functional MDM2.

Tumors tend to protect genes that are essential or beneficial for their growth, often by amplifying them. Gordion assessed whether MDM2 accumulates more amplifications than other genes on the chromosome arm, as this could indicate that increased MDM2 activity provides a growth advantage to that cancer type.

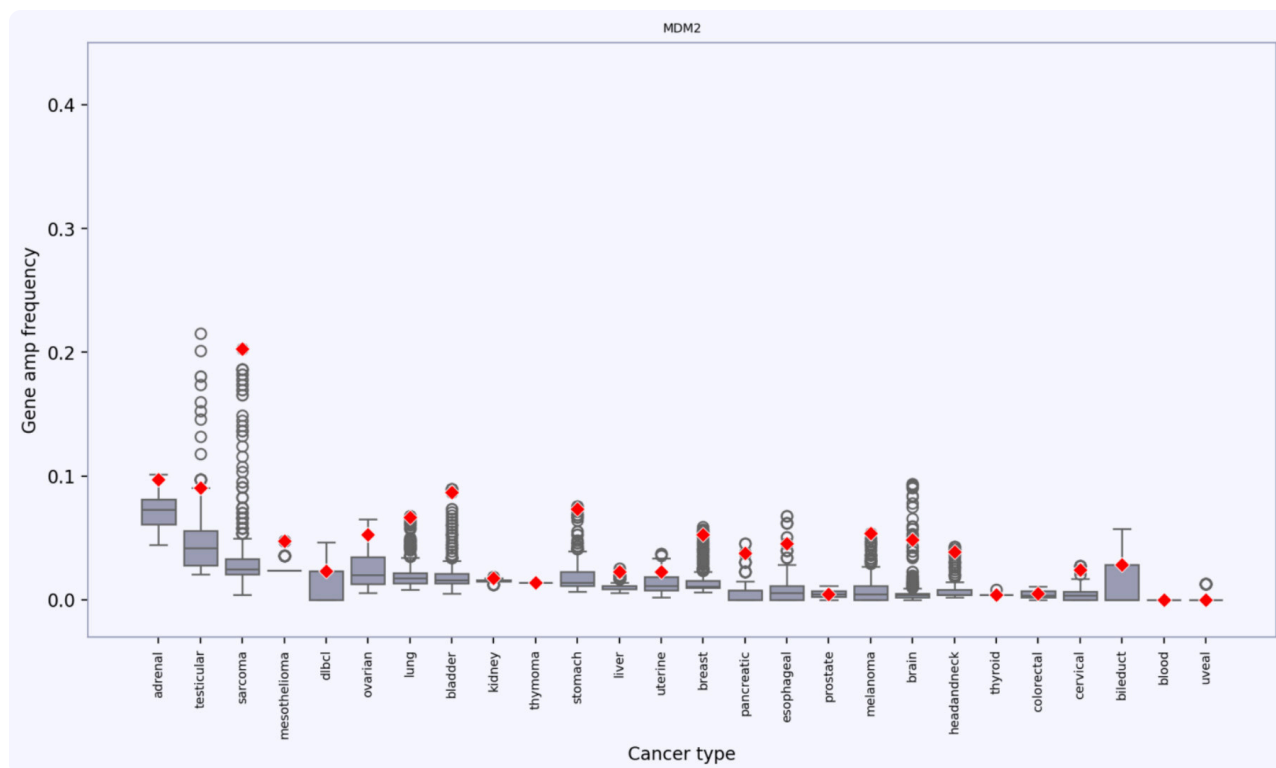


Figure 4. The importance of MDM2 in different tumors is illustrated by the difference between the median gene amplification across the chromosome arm (the horizontal line on the bar plots) and MDM2 gene amplification represented by a red diamond.

In most tumor types, MDM2 is amplified more frequently than other genes on chromosome arm 12q. An extreme example is sarcoma, where MDM2 amplifications exceed 20%. The high prevalence of MDM2 amplification and its role as the primary driver of 12q gains suggest its attractiveness as a therapeutic target.

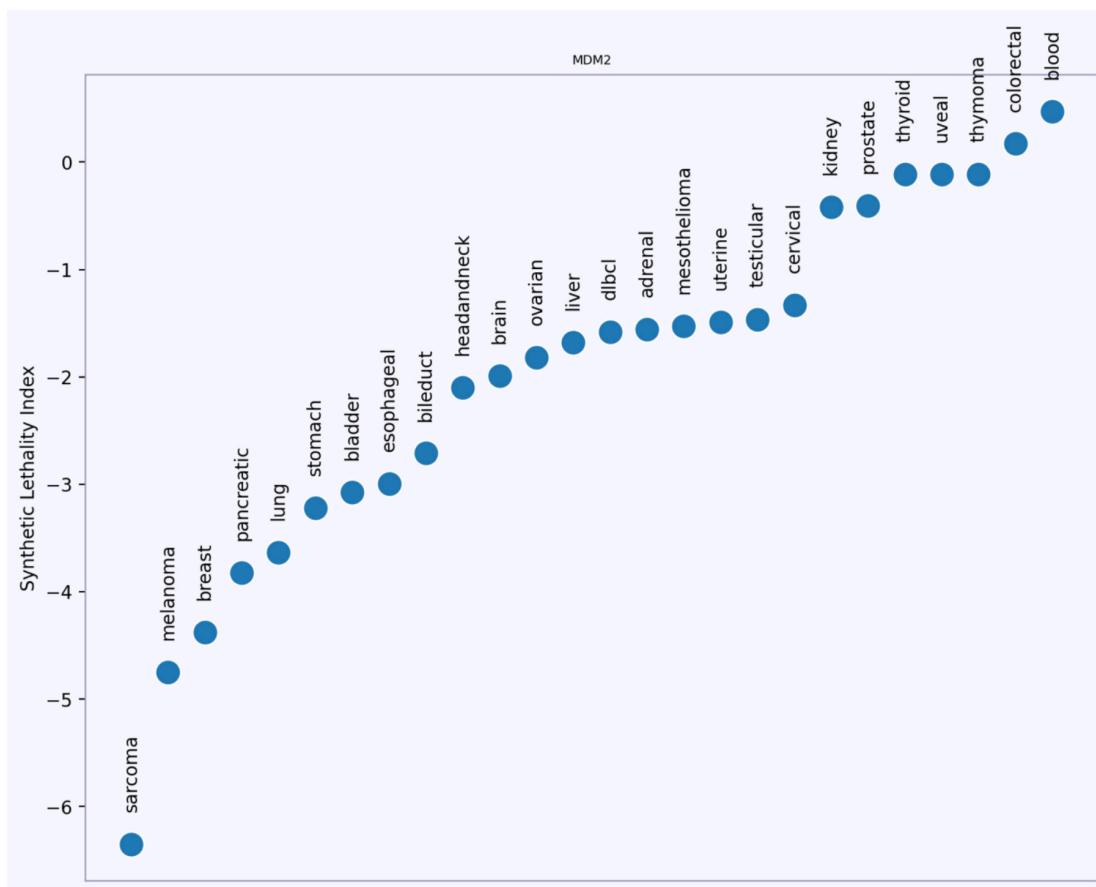


Figure 5. The Synthetic Lethality Index integrates gene loss and amplification patterns to quantify MDM2 essentiality across different tumor types. Lower SL Index scores correspond to higher tissue dependency on MDM2. These metrics enable the identification of tumors most vulnerable to MDM2-targeted inhibition.

Good drug targets are lost less frequently than average genes, but are amplified more often than the chromosome arm average. By integrating these two observables, Gordion developed a metric named the Synthetic Lethality Index (SL Index), which enables the identification of tissues where MDM2 essentiality is highest, with lower SL Index scores indicating greater essentiality. Notably, sarcoma, melanoma, and breast tumors exhibit the highest MDM2 essentiality. In these cancers, MDM2 is frequently amplified and rarely lost compared to the average gene on the same chromosome arm, indicating that these tumor types are less tolerant of MDM2 loss. This finding, together with results presented in Fig. 2, suggests the existence of patient subcohorts highly dependent on MDM2, in which MDM2 inhibitors could deliver high clinical efficacy.

IDENTIFICATION OF THE GENETIC BACKGROUND FOR MDM2 INHIBITION

In the detailed genetic analysis, we focused on sarcoma and breast (precisely, on estrogen-dependent breast cancers (Breast ER+)), as these two tumor types demonstrate the strongest enrichment of high MDM2 amplifications, making them prime candidates for MDM2-targeted therapies.

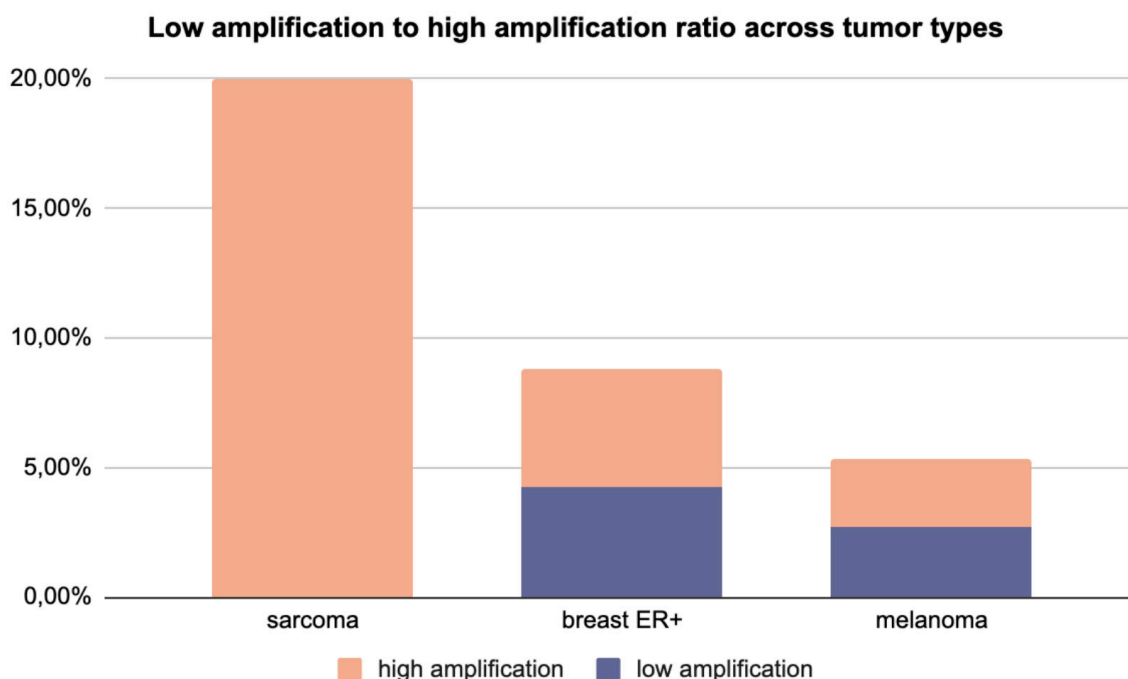


Fig. 6. The ratio of high amplifications and low amplifications in sarcoma, ER+ breast tumors, and melanoma. Bar colors represent the ratio of high amplifications to low amplifications. High amplifications (more than 6 extra copies) are marked in orange, and low amplifications (2-6 extra copies) are marked in blue.

1. Increased essentiality of MDM2 in TP53 wild-type sarcomas

The tumor type exhibiting the highest MDM2 essentiality is sarcoma. We assessed the genetic context in which this dependency is most pronounced and found that MDM2 upregulation occurs in 100% of TP53 wild-type sarcomas ($p\text{-value} = 1 \times 10^{-12}$). This finding aligns with earlier reports that, in tumors retaining wild-type p53, MDM2 amplification is the main safeguard against p53-driven apoptosis and cell-cycle arrest (2,3,4). By tagging p53 for degradation, amplified MDM2 effectively shuts down the tumor suppressor pathway, creating a vulnerability: sarcoma cells rely on continuous MDM2 activity to survive. This highlights MDM2 inhibitors as a promising precision therapy in this aggressive cancer.

Market size for TP53 wild-type sarcomas

The market size for TP53 wild-type sarcomas in the US is defined by approximately 40% of all sarcoma cases. With about 17,370 new sarcoma cases yearly, this means roughly 6,948 new patients annually.

2. Increased essentiality of MDM2 in ER+ breast cancer

The tumor type in which MDM2 also shows strong essentiality is breast cancer. Given the substantial heterogeneity of these tumors, which alters selective pressure on specific signaling pathways and oncogenic drivers, we assessed MDM2 essentiality separately in ER-positive, HER2-positive, and triple-negative breast cancer subtypes. Our analysis revealed the strongest MDM2 dependency in ER-positive tumors, notably independent of TP53 status (p-value = 0.46). This is intriguing as it suggests other dependencies of MDM2 independent of p53, or the existence of a resistance mechanism that eliminates breast tumor dependency of MDM2 and TP53.

RESISTANCE MECHANISMS FOR MDM2 INHIBITION

After identifying the cohorts most sensitive to MDM2 inhibition (TP53 wild-type sarcoma and ER+ breast cancer), but then finding that in breast cancer p53-MDM2 dependency is not present, we conducted an analysis to uncover potential resistance mechanisms that could explain this observation. Gordion AI identified two ubiquitous mechanisms that could negate the therapeutic effects of MDM2 inhibitors:

1. Upregulation of MDM4 to compensate for MDM2 blockade

MDM2 has only one paralog: MDM4. MDM4 and MDM2 both bind the p53 transactivation domain, they play distinct yet complementary roles in p53 regulation (10). Unlike MDM2, which acts as an E3 ubiquitin ligase targeting p53 for proteasomal degradation, MDM4 lacks intrinsic ubiquitin ligase activity and instead directly inhibits p53's transcriptional activity (10, 11).

Using patient tumor data, we analyzed the relationship between MDM2 and MDM4 in TP53-mutant and TP53-wild-type samples. In most cancer types, MDM4 is co-amplified alongside MDM2. This suggests that the resistance against potential MDM2 inhibitors is already present in tumors even before treatment with MDM2 inhibitors. The notable exception to the presence of MDM4 amplifications is sarcoma: unlike other cancers, where chromosome 1 (harboring MDM4) is frequently amplified, sarcomas rarely exhibit chromosome 1 amplification, and do not show MDM4 upregulation, hence it is likely explanation for why MDM2 is so relevant in this issue. On the other hand, MDM4 is extremely frequently amplified in breast tumors, explaining the low p-value for MDM2-TP53 dependency. Hence, breast cancer has an existing resistance mechanism, reducing the attractiveness of this tissue for MDM2i development. In conclusion, MDM4 upregulation should be considered as a ubiquitous and pre-existing resistance mechanism that will reduce the clinical response rates for MDM2 inhibitors.

2. Acquisition of TP53 point mutations

In the analyses above, we demonstrated a strong relationship between MDM2 essentiality and TP53 status: in TP53 wild-type tumors, MDM2 becomes critically important for tumor progression, particularly when MDM4 is not amplified. MDM2 upregulation drives p53 degradation, abrogating its tumor-suppressor function (6). Consequently, p53-downregulated tumors proliferate more rapidly but also accumulate additional mutations, with TP53 itself being the gene likely to be frequently mutated (12,13).

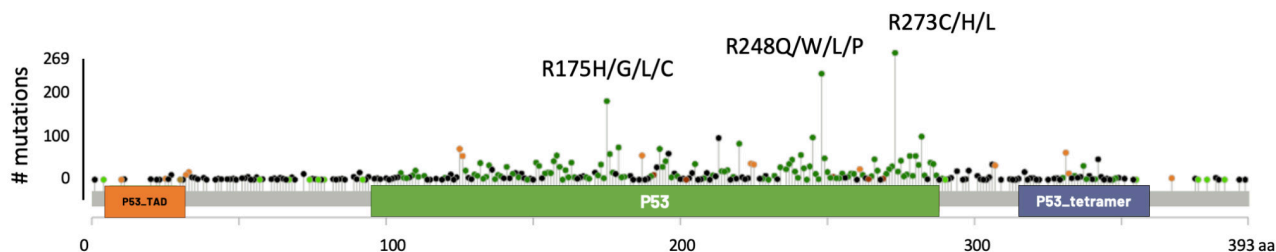


Fig. 7. TP53 is the most frequently mutated gene in cancer. Gene Mutation Map presenting the distribution of point mutations across the TP53 gene sequence. Green pins – missense mutations; black pins– truncating mutations; brown pins – in-frame indels; violet pins – others. The highest green pins mark a hotspot mutation.

Hence, MDM2 activity increases the accumulation of point mutations in TP53. We assessed whether heterozygous TP53 point mutations influence MDM2 upregulation and found that the selective pressure on MDM2 in tumors harboring heterozygous hotspot TP53 mutations mirrors that in tumors with complete TP53 loss. This suggests that a single point mutation within p53 might completely abrogate MDM2 inhibition driven response rates. The paradox is that MDM2 inhibitors will “induce” mutagenesis of p53 gene.

Validation experiments

The observed link between TP53 wild-type sarcomas and MDM2 dependency has been extensively documented in the literature and explored both experimentally and in clinical trials (NCT01877382, NCT03217266; 14,15,16).

To confirm identified resistance mechanisms of MDM2 inhibition (both MDM4 upregulations and p53 point mutations), we propose an experiment using engineered cell line models. This experiment could be conducted by our partner, VUS Genetics, a CRO with extensive expertise in gene editing and functional assays.

The experiment will employ six isogenic human cancer cell lines to assess how TP53 status and MDM4 co-amplification influence sensitivity to an MDM2 inhibitor in a viability assay:

1. TP53 null – Complete loss of TP53 (framework for MDM2-independent survival).
2. TP53 wild-type – Endogenous, functional TP53 as a comparator for p53-mediated response.
3. TP53 wild-type + MDM4 amplification – Wild-type TP53 with engineered MDM4 copy number increase to mimic compensatory inhibition of p53 when MDM2 is blocked.
4. TP53 hotspot heterozygous missense mutants – Each line carries one allele of TP53 mutated at a classic p53 hotspot residue, with the second allele remaining wild-type:
 - R175X (arginine → chosen amino acid at 175)
 - R248X (arginine → chosen amino acid at 248)
 - R273X (arginine → chosen amino acid at 273)

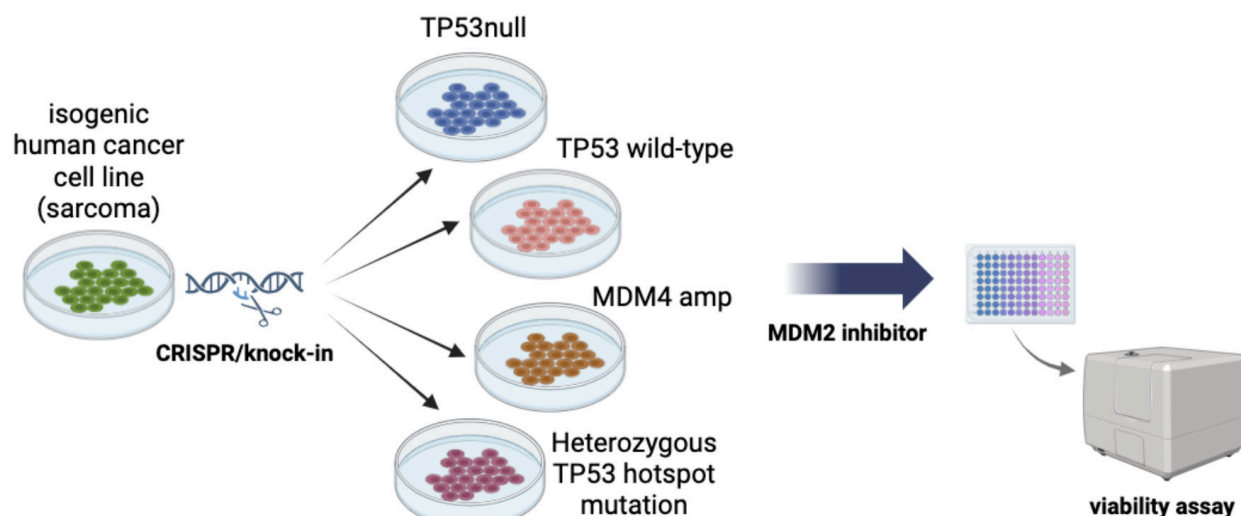


Fig. 8. Validation experiment for identified dependency in sarcoma and possible resistance mechanisms.

Rationale

- TP53 null vs. wild-type Establishes baseline dependence on MDM2 when p53 is absent versus intact.
- MDM4 amplification in TP53 wild-type Tests whether elevated MDM4 provides resistance by functionally substituting for MDM2.
- Heterozygous TP53 hotspot mutants Models early resistance mutations arising under MDM2 inhibition in initially TP53 wild-type tumors.

Breast cancer patient sub-population likely to respond to MDM2 inhibition.

In a hypothesis free approach, we investigated the effect of the genetic mutations affecting MDM2 essentiality in breast tumors. Two strategies were deployed to identify genes increasing/decreasing the essentiality of MDM2:

- i) We search for the genetic context where **MDM2 amplifications are overrepresented, suggesting tumor dependence on high levels of MDM2 protein.**
- ii) We search for the genetic context where **the loss of MDM2 is underrepresented, suggesting susceptibility to MDM2 inhibition.**

We explored a scenario where a mutation in a different gene leads to increased MDM2 essentiality, resulting in elevated rates of MDM2 amplifications or lack of the MDM2 losses. Alternatively, in cells susceptible to MDM2 inhibition, the loss of even a single copy should be poorly tolerated. We analyzed which alterations are good predictors of the absence of MDM2 mono-allelic losses. We hypothesize that these mutated genes could serve as biomarkers for a cohort in which MDM2 inhibition might be more effective. To identify such genes and mutations, we performed a comprehensive analysis of the breast cancer cohort, quantifying MDM2 amplification or loss depletion frequencies in tumors harboring specific gene mutations

We considered three types of gene alterations for co-mutated genes (biomarker candidates):

- First, a bi-allelic loss of a gene, where all copies of a gene are lost. Genes that lose both copies in at least 1% of tumors were considered.

- Second, some genes are known to be haploinsufficient and a mutation in one copy already confers a beneficial effect on tumor growth (9,10). For a predefined list of such genes, we considered tumors with mono-allelic loss of such genes. The list was enriched in genes involved in DNA repair processes. Gordion is using a proprietary list of haplosuppressors (details in the Supplementary Materials).
- Third, we used gene activations, defined as genes with gain-of-function mutations or amplifications.

To test the relationship of a potential biomarker with the rate of MDM2 amplification or loss depletion, for each biomarker, we divided the tumors into two groups: biomarker-mutated (e.g., bi- or mono-allelic loss (combined SNV, SV, indels, deletions), or amplified) and non-mutated. A logistic regression model was built to predict MDM2 amplification or loss depletion based on the biomarker status and a confounding variable - the overall rate of MDM2 amplification or loss depletion in the tumor. P-values and odds ratios (OR) were used to prioritize the candidate biomarkers. For an optimal biomarker, a high OR, a low p-value, and a large cohort size are expected.

RESPONSE BIOMARKERS	GENE SYMBOL	GENE ALTERATION	CHR. ARM	OR [CI]	P-VALUE	COHORT SIZE
	IGF1R	amplified	15q	3.86 [1.82-8.16]	0.0004	4%
	CCND1	amplified	11q	3.17 [1.65-6.06]	0.0005	9%
	ESR1	amplified	6q	3.88 [1.48-10.15]	0.005	16%
	PTPRD	bi-allelic loss	9p	3.0 [1.08-8.36]	0.04	2%
	ARID1A	bi-allelic loss	1p	3.97 [1.09-14.54]	0.04	1%

Table 1. A list of genes positively associated with **MDM2** (only genes with OR > 3; p-value < 0.05 are shown). OR - odds ratio; CI - confidence interval; Cohort size is the percentage of tumors with a given gene alteration present in **breast patient samples**.

The strongest biomarker identified is IGF1R amplification (OR = 3.86, p = 0.0004). This observation aligns with literature demonstrating that MDM2 acts as an E3 ubiquitin ligase that directly ubiquitinates and degrades IGF1R (17). However, MDM2 inhibition presents a therapeutic paradox: while activating p53-dependent apoptosis, it simultaneously increases IGF1R protein stability, leading to enhanced IGF1R-driven pro-survival signaling. Consequently, IGF1R-amplified tumors might require combination therapy targeting both MDM2 and IGF1R pathways, as MDM2 monotherapy alone may be insufficient in this biomarker-defined subset.

A similarly strong correlated biomarker is CCND1 amplification (OR = 3.17, p = 0.0005), which demonstrates an analogous mechanistic relationship. CCND1 (cyclin D1) is a direct substrate for MDM2's E3 ubiquitin ligase activity (18). MDM2 inhibition in CCND1-amplified tumors paradoxically leads to cyclin D1 stabilization and further dysregulation of cell cycle checkpoint control. This creates a reciprocal resistance mechanism where p53-dependent apoptotic activation is counteracted by enhanced cyclin D1-driven cell cycle progression. Therefore, CCND1-amplified tumors similarly might require combination approaches pairing MDM2 inhibitors with inhibitors to simultaneously eliminate pro-apoptotic signaling while preventing compensatory cell cycle dysregulation.

ESR1 (Estrogen Receptor Alpha) positivity emerges as a significant biomarker in breast cancer (OR = 3.88, $p = 0.005$). ER α transcriptionally upregulates MDM2 through direct binding to estrogen response elements, establishing ER α -positive tumors with elevated baseline MDM2 levels (19). ER-positive breast cancers with concurrent MDM2 amplification represent a high-value population for MDM2 inhibitor therapy. Additionally, ER α -targeting therapies (fulvestrant, tamoxifen) reduce MDM2, suggesting synergy between endocrine therapy and MDM2 inhibitors in this disease subset.

ARID1A loss (OR = 3.97, $p = 0.04$) according to literature demonstrates synthetic lethality with MDM2-p53 pathway inhibitors. ARID1A-deficient cells exhibit dramatically increased sensitivity to MDM2 antagonists through mechanisms involving decreased p21 expression, increased proapoptotic signaling (PUMA, NOXA), and impaired DNA damage repair (20). This interaction is p53-dependent and represents strong predictor of MDM2 inhibitor efficacy.

We also identified a relation with PTPRD loss (OR = 3.00, $p = 0.04$), however no direct relationship with MDM2 has been documented in the literature.

Biomarkers demonstrating a strong inverse association with MDM2 (OR < 0.15) were designated as candidate resistance markers. In the presence of these alterations, MDM2 is more often lost than expected, leading us to hypothesize that MDM2 might not be particularly important for the survival of these tumors.

RESISTANCE BIOMARKERS	GENE SYMBOL	GENE ALTERATION	CHR. ARM	OR [CI]	P-VALUE	COHORT SIZE
	CDKN1B	bi-allelic loss	12p	0.08 [0.02-0.29]	0.0001	1%

Table 2. A list of genes negatively associated with **MDM2** (OR < 0.15; p -value < 0.2) – potential resistance biomarkers. OR – odds ratio; CI – confidence interval; Cohort size is the percentage of tumors with a given gene alteration present in **breast patient samples**.

Only CDKN1B met the criteria as a relevant biomarker (OR = 0.08, $p = 0.0001$).

These dependencies and the cross-dependencies between TP53 and in-between the above biomarkers should be used to design effective patient stratification strategies.

Full results remain a confidential property of Gordion Bio.

CONCLUSIONS

Gordion's analysis revealed that MDM2 exhibits the characteristics of a highly effective therapeutic target. Our findings are consistent with preclinical data and the results of CRISPR screens across various cell-line models.

To assess commercial opportunity, we performed comprehensive pan-cancer dependency profiling, which showed that sarcomas and breast cancers are the tumor types reliant on MDM2 function. Further examination of these cohorts identified subgroups with high MDM2 dependency: TP53 wild-type sarcomas and ER-positive breast cancers.

However, in-depth analysis of patient data uncovered two primary resistance mechanisms to MDM2 inhibition: upregulation of MDM4 and acquisition of TP53 point mutations. Both these mechanisms are less frequently observed in sarcomas, explaining their greater sensitivity to MDM2 inhibition.

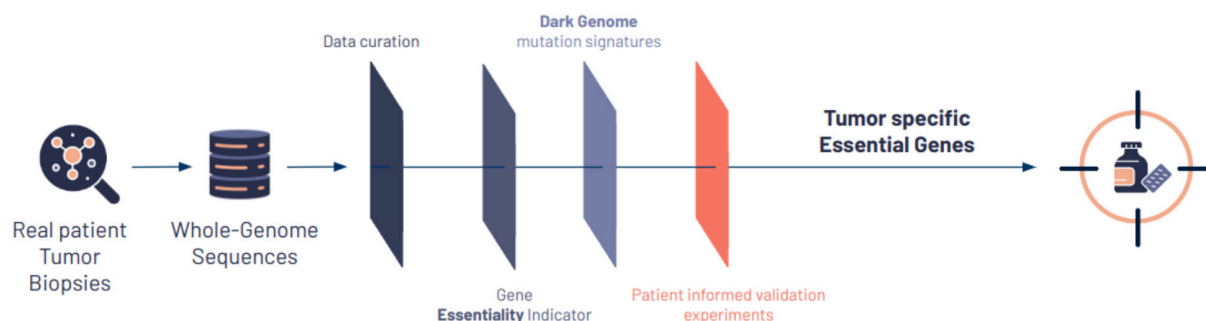
Biomarker analysis in breast cancer identified multiple sub-populations for MDM2i therapy, beyond simple TP53 status. The strongest biomarkers are: ESR1 amplification, ARID1A loss, CCND1 and IGF1R amplification. The cross-dependencies between all biomarkers and the tissue specificity of particular MDM2 dependency should reveal the best patient stratification strategies for individual tissues.

In summary, pan-cancer dependency profiling analysis indicates that MDM2 is a highly promising drug target in significant patient cohorts. However, the ubiquity of resistance mechanisms reduces the likelihood of clinical success that could be counterbalanced by sophisticated patient selection strategies and synergistic drug combinations.

SUPPLEMENTARY INFORMATION

THE GORDION PLATFORM - OVERVIEW

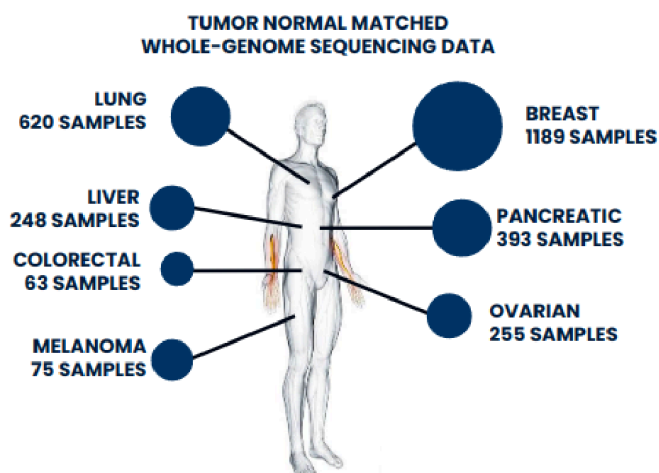
The Gordion Platform introduces an innovative method for evaluating oncology drug programs. By using the patient's whole genome data and harnessing the power of Machine Learning on the Dark Genome, it identifies essential genes specific to tumor types.



Supplementary Figure 1. Gordion Platform overview.

The Data

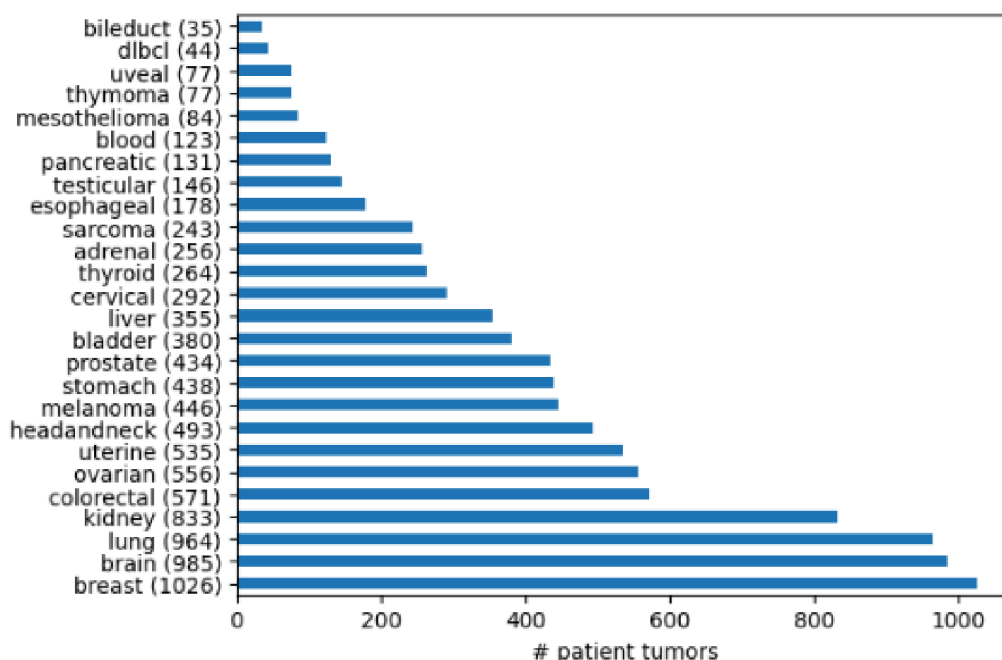
Gordion's platform is built on top of thousands of carefully selected and uniformly processed patient tumor whole genomes. These span 7 cancer types: breast, lung, ovarian, liver, pancreatic, colorectal, and melanoma, supported by 9,996 whole-genome CNV profiles from 26 tumor types.



Supplementary Figure 2. Tumor types and quantity of samples in the WGS Database.

- WGS Database - The 2,607 tumor-normal matched whole genome datasets are split between 7 cancer types (breast, ovarian, pancreatic, lung, colorectal, melanoma, and liver). All have been sequenced on the Illumina platform using paired-end reads with an average depth of 30-60x (tumors) and 25-60x (normal tissue). Samples have fully characterized genetic mutation profiles, including single-nucleotide variants, in-dels, copy number alterations, and structural changes.

- CNA+WES Database - whole-genome CNV combined with whole-exome sequencing data profiles for 9,966 tumor genomes across 26 cancer types. The raw data were originally produced by The Cancer Genome Atlas (TCGA) and were processed with the ASCAT3 tool.



Supplementary Figure 3. Tumor types and quantity of samples in the 10K CNA Database.

Data pre-processing and quality control

To build a large collection of tumor genomes across different cancer types, we aggregated datasets from multiple sources. These data sources have different application processes, as well as data storage/retrieval mechanisms. All three major repositories of genomic data have proprietary tools for accessing it: `gdc` tool is used to download data from TCGA; `score` from ICGC; and `pyEGA3` for downloading data deposited in EGA.

Due to specific research problems addressed by academic projects, data generated by diverse research groups, also as part of one consortium, can substantially differ in the study design, data processing methods, and format of the released data. Aggregation of such datasets requires extensive quality checks and uniform re-processing and typically results in excluding >10% of patient records. Adding a new dataset from a public repository to Gordion's database has often required solving project- or sample-specific problems with the downloaded raw data.

The typical input data for the WGS processing pipeline is the raw output of the DNA sequencer - short sequences (reads) in the FASTQ format. The WGS data deposited into repositories is often aligned reads (BAM or CRAM format). The alignments can be prepared in different ways, using different reference genomes, and this has a critical effect on the downstream processing.

To maintain uniformity of the results on Gordion's Platform, we re-align all data that is released in BAM or CRAM formats. Processing such datasets starts with the extraction of raw reads and base quality values (in the form of two FASTQ files) from the original BAM or CRAM files, and is described in the section below

Extraction of reads from alignment files

First, the BAM or CRAM file is checked against invalid reads that may break the downstream processing. In the case of CRAM input, the exact reference genome file that was used for the alignment must be identified to facilitate processing. The filtered alignment files are reindexed and subjected to read extraction using Bazam. Using this tool allowed us to avoid costly read-sorting (input alignments are sorted by genomic coordinates, and FASTQ files require name-sorted reads) and a very large intermediate file, saving both compute and storage costs.

As a result of Bazam processing, the reads from the BAM/CRAM file are split into a pair of gzipped FASTQ files containing read “mates”. Next, the reads in the FASTQ files are trimmed to remove low-quality and adapter sequences. Samples with coverage depth greater than 62x undergo random downsampling to ~60x. A fixed random seed is used to facilitate the reproducibility of this process. Finally, data quality is analyzed and saved in QC reports.

PURPOSE(S)	SOFTWARE	REFERENCE
Alignment manipulation	Samtools 1.12	Danecek et al., 2021
Alignment validation		
Read indexing		
Read extraction from coordinate-sorted BAM	Bazam 1.0.1	Sadedin and Oshlack, 2019
Read quality trimming	Fastp 0.20.1	Chen et al., 2018
Read subsampling	Seqtk 1.3-r106	Github link
FASTQ quality control	FastQC v0.11.9	Andrews, 2010
QC report aggregation	MultiQC v1.10.1	Ewels et al., 2016

Supplementary Table 1. Tools used for WGS data pre-processing and quality control.

Sample eligibility criteria

To maintain a high-quality level of the data on the platform, we require that the added samples meet certain criteria. Depending on the data source and available information, some of them can help in the identification of non-eligible samples up-front, while others lead to sample exclusion after pre-processing (e.g., low read count) or only after processing with our WGS analysis pipeline (e.g., uniformity of coverage). Examples of the criteria required include:

- Fresh-frozen material
- Paired-end Illumina sequencing with at least 75bp long reads
- Mean tumor genome depth after deduplication $\geq 30x$
- Mean normal genome depth after deduplication $\geq 25x$
- Percent of the normal genome covered by at least $20x \geq 80\%$
- Percentage of mapped reads $>90\%$
- Tumor purity $\geq 20\%$
- germline variants between 4M and 5.5M

- somatic variants within expected ranges for the tumor type

The WGS analysis pipeline

The whole genome sequencing (WGS) pipeline maps the short reads to the reference genome and detects and genotypes all kinds of genetic variants – substitutions, short indels, copy number alterations, and other structural variants, both somatic and germline. All variants are quality-filtered and annotated. Quality control (QC) metrics are generated at all stages of the processing.

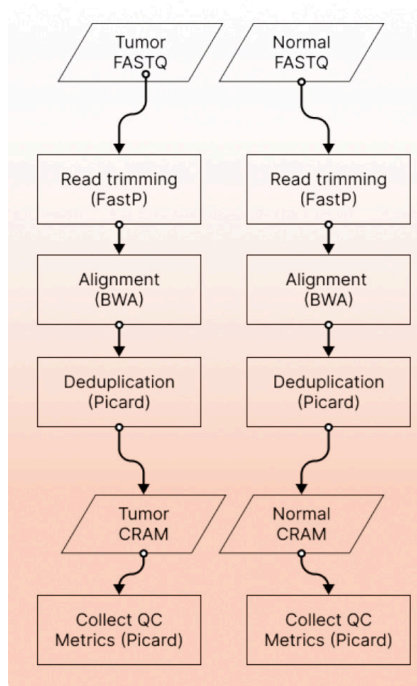
The WGS pipeline allows for processing sequencing data from pairs of matched tumor and normal samples. It also implements an experimental tumor-only mode. It is optimized for data from Illumina platforms and has been validated in the analysis of >6000 genomes with a mean genome coverage of 30-60x.

Description of the pipeline is divided into two stages:

- alignment stage that takes as input reads in FASTQ format, maps them to the reference genome (GRCh37), and post-processes the alignment file, producing a CRAM file ready for subsequent analysis
- variant calling and annotation stage, which uses a matched pair of produced CRAM files and generates a set of annotated variant files (VCF)

Alignment

Reads, provided in FASTQ files, are optionally trimmed and mapped to the GRCh37.d5 reference genome by the de facto standard in such applications BWA-MEM algorithm. The resulting alignment is sorted by genomic coordinates. Duplicate reads are marked using Picard, and the output is saved to a CRAM file and indexed. After the CRAM has been created, coverage statistics are calculated, and a QC analysis is performed using Picard's CollectMultipleMetrics function. The QC statistics are saved to a report file in a PDF format, and in tab-delimited files for machine processing, e.g., flagging low-quality alignments.



Supplementary Figure 4. Alignment workflow.

PURPOSE(S)	SOFTWARE	REFERENCE
Read quality trimming	Fastp 0.20.1	Chen et al., 2018
Read mapping		Li, 2013
Alignment indexing		Danecek et al., 2021
Read sorting Duplicate marking Alignment QC	Picard 2.22.4	
Depth of coverage	mosdepth 0.3.2	Pedersen and Quinlan, 2018

Supplementary Table 2. Tools used for the alignment.

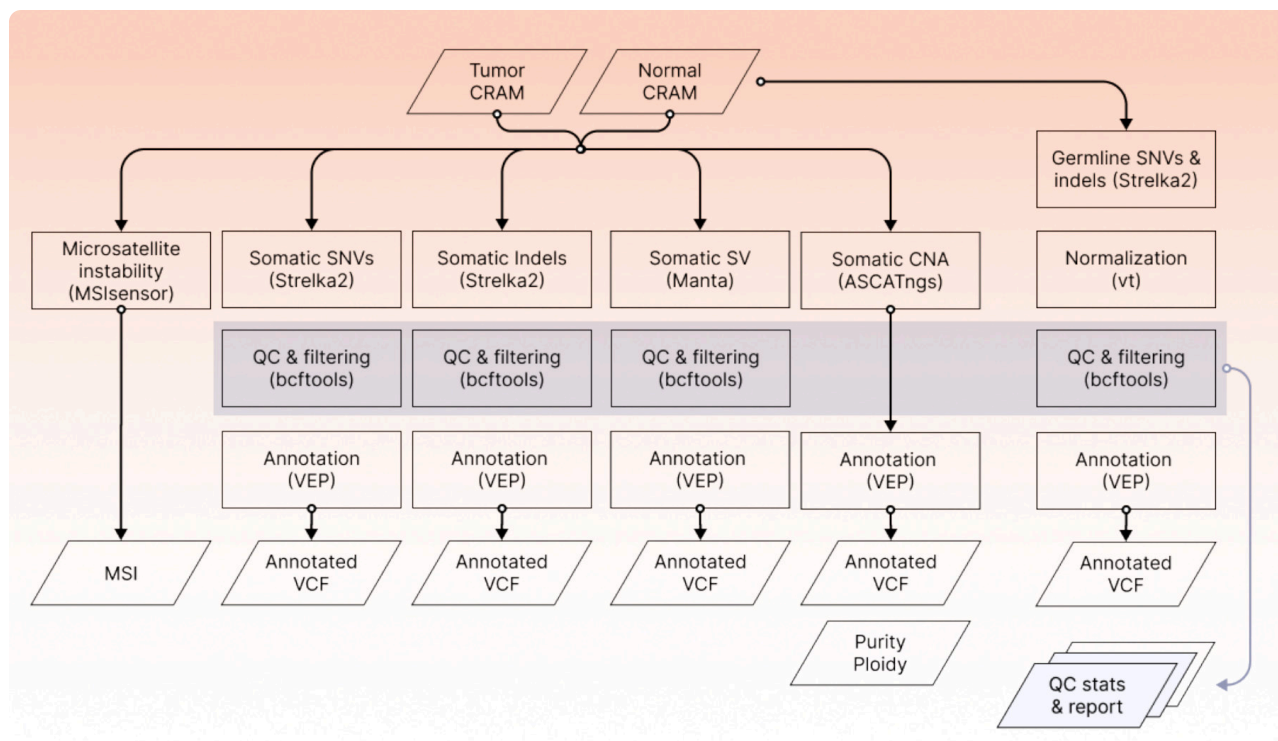
Variant calling

Our variant calling pipeline can work in either of two modes: matched tumor-normal analysis or tumor-only analysis. The latter has been used experimentally only and all data in our platform are based on a tumor-normal matched workflow.

Matched tumor-normal analysis

The matched analysis uses as input a pair of tumor and normal alignment files (BAM or CRAM) generated by the alignment workflow. By contrasting the tumor alignment with its matched normal alignment as a reference, individual algorithms detect changes in the tumor DNA (somatic variation). Five categories of variation - microsatellite instability (MSI), substitutions (SNVs), short indels, structural variants (SVs), and copy-number alterations (CNA) - are detected independently of each other by dedicated tools. Where applicable a quality control and filtering step (low-quality variants are removed) is performed. All variants passing quality criteria are subject to annotation, with (among others) Clinvar, population allele frequencies (1000 Genomes, ExAC, gnomAD, and two in-house databases of cancer patients), and various pathogenicity scores (e.g., SIFT, PolyPhen, DANN).

The pipeline detects and annotates germline variation as well. In the process, only the germline alignment file is used. Since germline substitutions & indels frequently contain multiallelic variants, for the purpose of annotation, these are decomposed and normalized. Next, similarly, as for somatic variant detection, the variants are filtered and annotated.



Supplementary Figure 5. Matched tumor-normal analysis workflow.

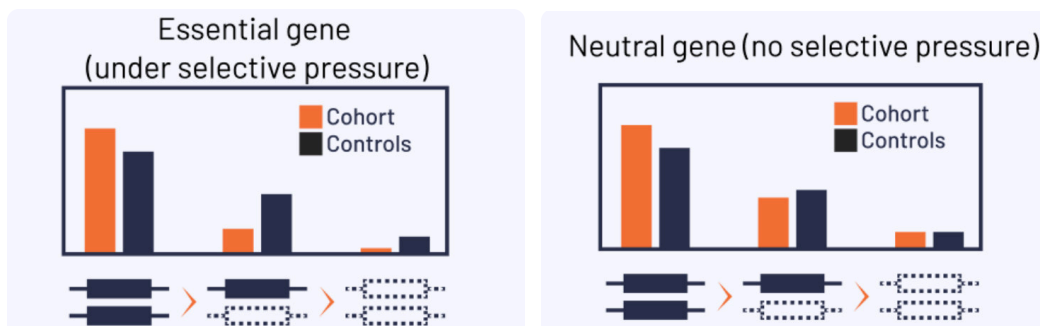
Individual algorithms used in the pipeline are implemented in open-source, commercially available software. They represent state-of-the-art methods used in projects published in top-tier journals (e.g., PCAWG). Two of the tools (i.e., Strelka and Manta) were co-developed by Illumina Inc. and have laid the foundation for the Illumina Dragen Platform. The detailed list of tools is presented in the table below.

PURPOSE(S)	SOFTWARE	REFERENCE
Detection of: • Somatic SNV/indels • Germline SNV/indels	Strelka 2.9.10	Kim et al., 2018
Detection of: • CNA segments • Purity • Ploidy	ASCAT v3.0.0	Van Loo et al., 2010
Detection of: • Somatic SV • Germline SV	Manta 1.6.0	Chen et al., 2016
Microsatellite instability	MSI sensor 0.6	Niu et al., 2014
Variant manipulation		
Variant QC & filtering	BCFtools 1.12	Danecek et al., 2021
Variant annotation	VEP 116	McLaren et al., 2016
QC report aggregation	MultiQC	

Supplementary Table 3. Tools used for the matched tumor-normal analysis workflow.

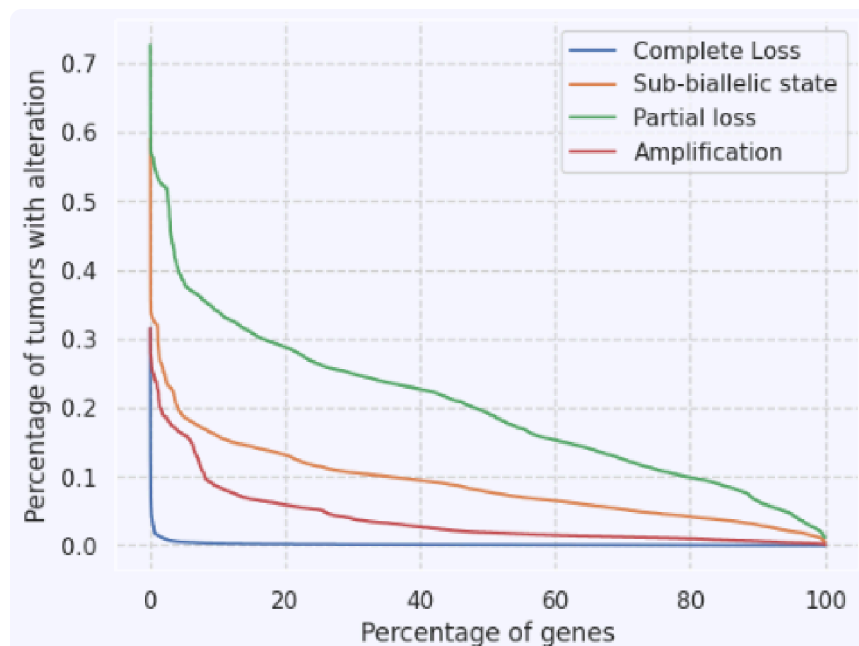
Partial loss

Essential genes are protected by the cell during tumor evolution. Looking at the rates of gene losses and amplifications, we can distinguish genes that are under positive selective pressure (essential genes; rarely lost/mutated) from the rest. Partial loss (pLOSS) of a gene is a concept adopted at Gordion to capture pressure on tumor cells to retain functional copies of essential genes. It allows us to measure selective pressure in all genes, including those that very rarely lose all copies.



Supplementary Figure 6. Selective pressure on essential and neutral genes.

Very few genes are lost completely (bi-allelic loss, also known as complete loss (cLOSS)) in a sufficient number of tumors to facilitate robust statistical analysis. This means that for the majority of genes, one would have to collect an infeasible number of tumor genomes to perform an analysis. However, partial losses (one or more copies) are much more frequent, with 80% of genes having lost at least a single copy of the gene in 10% of all the tumors in our database.



Supplementary Figure 7. Relationship between gene alterations and the number of affected tumors. For 80% of the protein-coding genes, at least 10% of Gordion's cohort (N=2607) has a partial loss. 40% of the genes are in the sub-biallelic state in at least 10% of the tumors. 20% of the genes have an amplification in at least 6% of the tumors, and only 19 genes (~0.5%) are completely lost in more than 10% of the tumors.

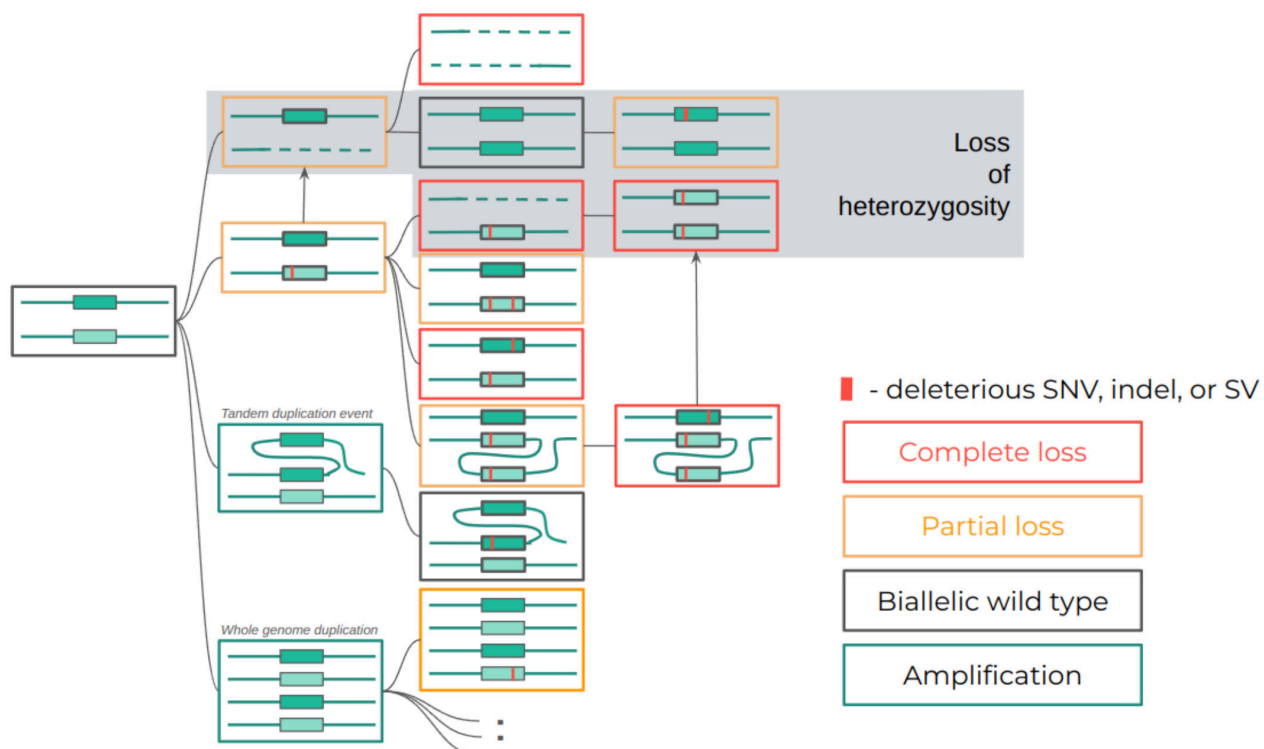
At Gordion, we have defined the concept of partial loss, also called single copy loss, as a state of the gene where the number of functional copies of the gene is below the average ploidy of the tumor. Gene loss leads to lower expression and reduced availability of the protein, which, in the case of essential genes, induces stress and lower cell fitness. In highly mutating tumor cells, it also exposes the cells to lethal complete gene loss, so it is eliminated by the tumor evolution. Depletion of partial gene losses (and enrichment of amplifications) is thus a marker of essentiality; one that can be measured for the majority of genes in cohorts of >100 patients.

On the DNA level, the function of a gene can be lost in multiple ways, for example:

- the presence of a protein-altering single-nucleotide variant (SNV) or a short indel,
- by large structural variants (SVs), affecting the gene sequence, promoters, or enhancers,
- by copy number alterations (CNA), including, e.g., copy-neutral loss-of-heterozygosity.

Gordion is also analyzing single-nucleotide variants and their effect on gene function. However, besides deciding whether a variant itself affects a protein's function, in tumors, one needs to take into consideration additional biological and technical factors:

- one or more alleles can be affected - more than half of tumors undergo a genome duplication event
- two mutations in one gene can be in cis (alter the same copy; one copy is lost) or in trans (each modifies a different copy; at least 2 copies are lost)
- germline and somatic alterations need to be evaluated jointly because variant detection tools subtract the germline variation as background from their results
- somatic mutations may affect the main clone (the majority of tumor cells) or be subclonal (only a fraction of the tumor cells carry the variant)
- sample purity - the fraction of tumor cells in the sequenced sample can vary between 20 and 100%



Supplementary Figure 8. Examples of loss events and selection of mutational trajectories leading to them.

Overall, the Loss of Function outcome is a product of the events mentioned above. Therefore, characterizing the number of functional gene copies in a tumor genome has been a tremendously complex, laborious, and error-prone process involving field experts, from geneticists to bioinformaticians. The analysis requires manual integration of the results from several variant callers, careful and time-consuming evaluation of each, and often dealing with contradictory evidence when comparing the event's overall impact.

We have solved this by creating a proprietary 'FunctionalCopyProfiler'. Utilizing in-house expertise gained from profiling hundreds of tumor genomes, we have developed a tool that combines results across the different variant callers we use. For both somatic and germline genomes, FunctionalCopyProfiler processes small variants (SNVs and indels detected by [Strelka2](#)), large structural variations (deletions, tandem-duplication, inversions, translocations, insertions; detected by [Manta](#)), and copy-number changes (ASCAT tool), all supplemented with rich functional annotations, and the tumor's ploidy and purity. FunctionalCopyProfiler can infer the number of functional and lost copies of all protein-coding genes in the cancer genome using a broad set of customizable expert rules.

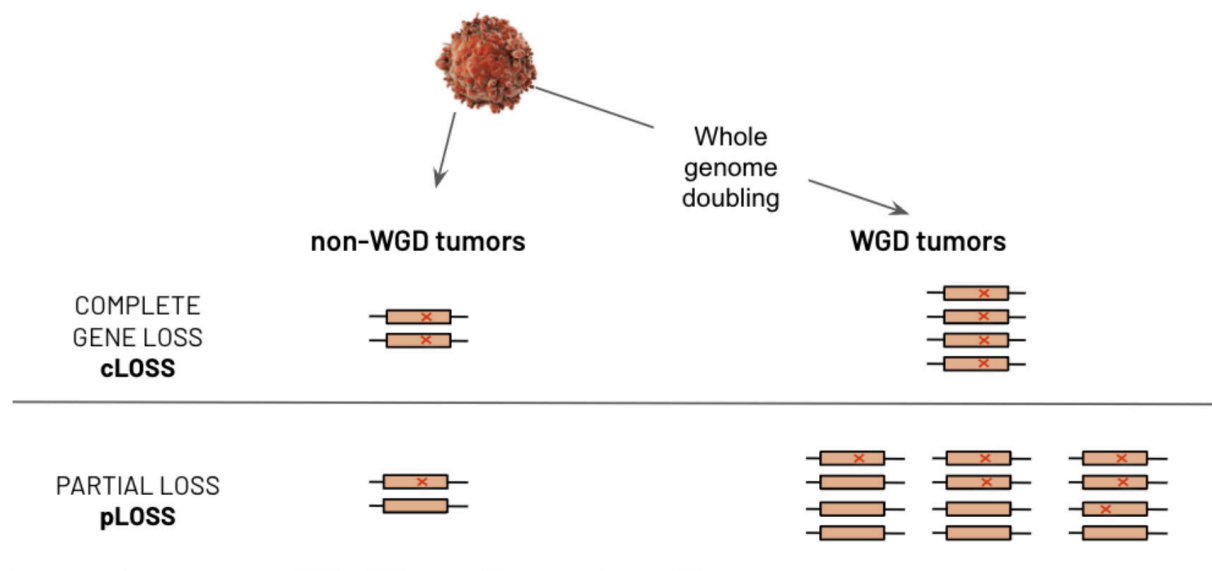
Not all pathogenic mutations lead to loss of function

A typical understanding of pathogenic mutation is that it ablates protein function. For the majority of the genes and phenotypes, this is correct; however, in many cases, the phenotype is caused by a gene's activation (KRAS, BRAF) or taking on a novel function (NPM1). Sometimes, the structural variants can lead to fusion genes, which encode hybrid proteins, affecting the cell's metabolism and fuelling the oncogenesis. There are also proteins where mutations, all classified in mutation databases as pathogenic, lead to either loss of function or gain of function, therefore eluding the commonly accepted division into oncogenes and tumor suppressor genes (TP53, DNMT3A). Such situations must be taken into account when classifying a gene as lost.

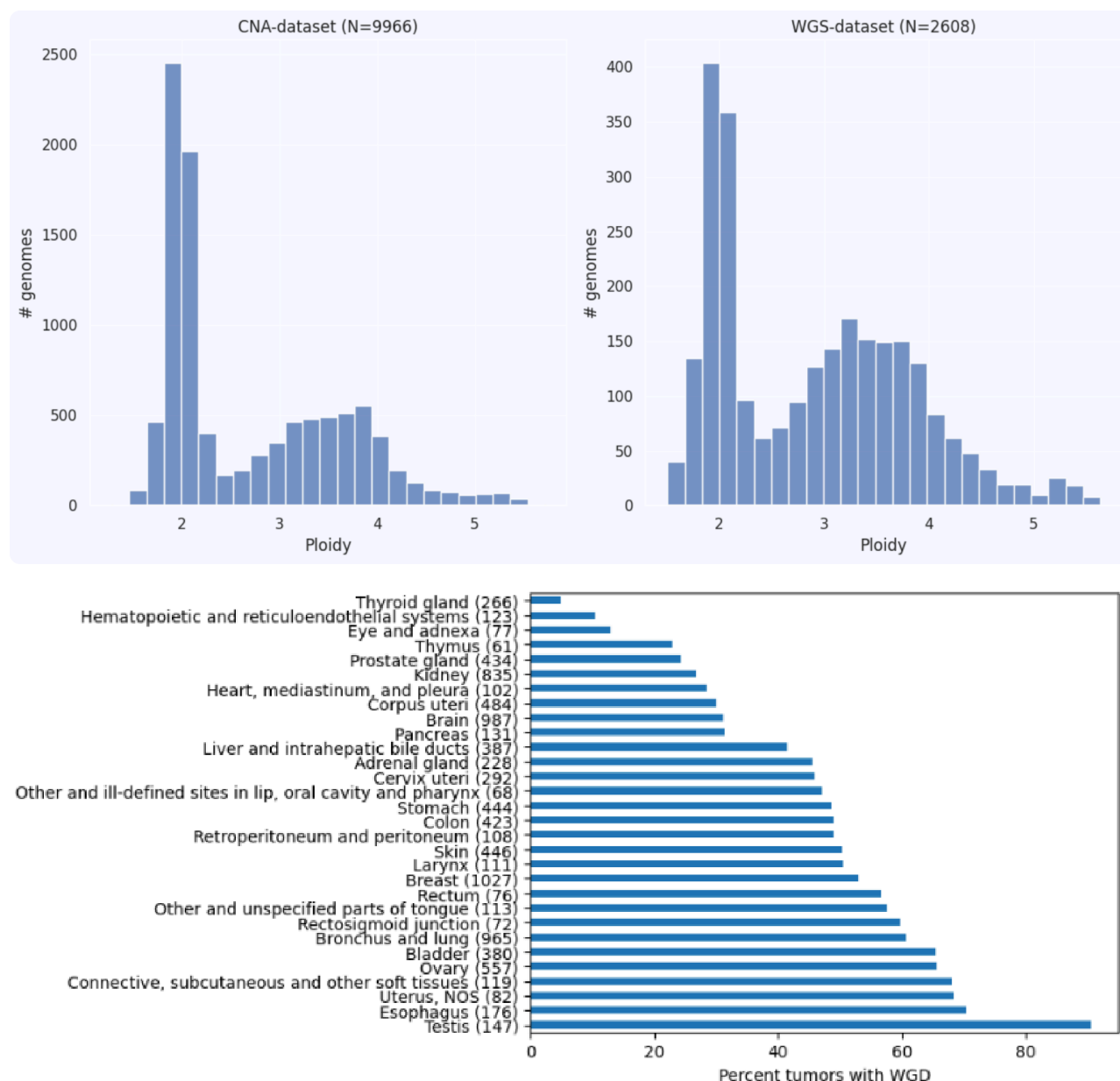
Mutations classified as pathogenic and acting via a mechanism different from protein function loss are not considered to lead to (partial) gene loss. For critical oncogenes (e.g., KRAS) and tumor suppressor genes (eg, TP53), the Gordion team created and maintains a manually curated list of mutations that are classified as loss-of-function (LOF), gain-of-function (GOF), and unknown. These classes of mutations are treated differently by the platform.

Whole Genome Duplication

Whole Genome Duplication (WGD), also known as polyploidy, is a biological phenomenon wherein an organism's entire set of chromosomes is duplicated. This process results in multiple copies of the genome within a cell or organism. While WGD is relatively rare in normal human cells, it has been observed to play a crucial role in the context of cancer, with over 50% of solid tumors undergoing WGD events. WGD results in multiple copies of the genome within a cell (in our data, 41% of tumors are diploid, 57% have undergone WGD, and 2% are classified as above $4n$). To address this challenge and properly quantify deletions, we consider deletions that remove one copy from a diploid tumor sample and deletions that remove 1, 2, or 3 copies from samples with ploidy ≥ 4 .



Supplementary Figure 8. Gordion utilizes different types of gene loss depending on tumor ploidy.



Supplementary Figure 9. Whole Genome Duplication in our data. The upper left panel shows a distribution of ploidy in the 10K CNA Database. Upper right in the WGS Database. The lower panel presents the percentage of tumors with WGD in different tumor types.

Understanding the implications of WGD becomes paramount when analyzing gene mutations in cancer for several reasons:

- Tumor Evolution and Heterogeneity.** WGD can contribute to tumor evolution and heterogeneity. The presence of multiple copies of the genome allows for a higher degree of genetic variation. This heterogeneity poses challenges in predicting the behavior of the cancer and devising effective treatment strategies.
- Impact on Mutational Landscape.** WGD influences the mutational landscape of a cancer cell. The increased genomic material provides more opportunities for mutations to arise, and certain mutations may be selectively advantageous, contributing to tumor progression and adaptability.

- **Therapeutic Implications.** The presence of WGD can affect the response to therapy. Tumor cells with duplicated genomes may exhibit altered sensitivity or resistance to certain treatments, making it crucial to consider WGD in the development of targeted therapies and personalized medicine approaches.

Accounting for WGD is essential for the accurate interpretation of genomic data. Failure to consider WGD may lead to misinterpretation of mutational profiles and hinder the identification of truly essential genes in the process of drug target ID. Gordion's partial loss, as well as gene amplifications, are calculated concerning the number of genome copies, taking into account genome doubling events.

Loss-of-function – our proprietary approach

Loss-of-function (LOF) of key genes is commonly used to stratify patients, for instance, to search for cohort-specific genomic biomarkers. Combining all types of variants is a very complex task, so the process typically involves only small variants (SNVs and indels). Even then, automation is far from trivial.

The information in mutation databases used for classifying loss-of-function mutations is frequently incomplete or conflicting. Sequencing artifacts lead to false positive variant calls, which are difficult to assess without inspecting the raw data. Accurate classification of loss-of-function cannot be done without expert curation. Our experts have performed manual curation of hundreds of tumors' whole genomes, going through mutation tables with extensive annotation, genome by genome. By cross-checking the variants' annotation with databases and publications, and inspecting the variants visually in the raw data, they interrogated several key cancer drivers and suppressor genes (e.g., TP53, KRAS, BRCA1, BRCA2), scrupulously annotating their mutational status in all samples. The extensive experience gained in this process allowed us to formulate a set of complex rules for the classification of variant combinations as loss-of-function events. Importantly, we have also specified rules that determine the lack of loss in cases that otherwise would result in false positive classifications. All these have been written down as an easily customizable set of "configurations" for FunctionalCopyProfiler.

The rules were then implemented directly in the tool to allow easier future changes both in variant detection algorithms, in variant annotations, and in the rules themselves. The initial version of the rules has been improved in several cycles of testing and benchmarking against a set of BRCA1 and BRCA2 losses in a group of over 800 breast cancer patients (created in the abovementioned manual profiling process). The current version yields 98.9% accuracy (96.2% sensitivity and 99.6% specificity) in classifying variants into three categories: complete-, partial-, and no-loss.

For each analyzed patient and gene, FunctionalCopyProfiler outputs the total number of copies and the number of functional copies, as well as auxiliary information on the mutations responsible for gene losses, and a degree of confidence in their classification. The statistics on the numbers of lost/functional copies aggregated over cohorts of patients are then used to measure the essentiality of genes.

GORDION AI MODEL

The Gordion AI stack integrates diverse analytical tools to evaluate multiple modalities of patient data. The model employs a suite of proprietary algorithms designed to detect novel molecular descriptors—unique patterns of mutations that may be associated with disease trajectory, tumor resistance, or specific molecular pathways.

Traditional analytical approaches face significant limitations when processing complex genomic patterns. The transformation of intricate descriptors into simplified features for conventional feature-based classifiers, or the reliance on domain-specific distance measures for distance-based classifiers such as Similarity Forests, results in substantial information loss. To address this challenge, we developed innovative techniques, including Random Similarity Forests: [Publication: Random Similarity Forests](#).

Prediction of expected gene copy number

The Gordion AI incorporates sophisticated tools to estimate expected gene copy number, a critical parameter for determining gene essentiality. While point mutations account for gene loss in fewer than 20% of cases, large-scale copy number variations (CNVs) are responsible for approximately 80% of gene losses. Depending on tumor type, specific chromosomal regions can be lost in 70-80% of tumors or amplified in up to 50%, providing compelling evidence of mutational pressure.

Large-scale CNVs play a fundamental role in determining gene essentiality. The extent of these alterations and their impact on gene dosage, focalization, and genomic context are key factors in distinguishing genes under strong selective pressure from those frequently lost or amplified as passenger events.

Comprehensive structural analysis beyond coding sequences

Our CNV analysis extends beyond standard approaches that focus primarily on coding sequences. We examine structural alterations across the entire genome, including large intergenic regions and intronic sequences, which can have significant regulatory consequences. Importantly, CNVs can influence enhancer activity, leading to dysregulated gene expression. A representative example is the identification of a specific amplification on chromosome 14q, which affects a super-enhancer associated with NKX2-1, a critical transcription factor involved in lung development and oncogenesis.

Driver gene identification from copy number alterations

Copy number alterations (CNAs) frequently affect large chromosomal fragments, often encompassing entire chromosomal arms or even complete chromosomes, making it challenging to pinpoint causal genes. By integrating mutational pressure across two modalities—CNAs and point mutations—we identify drivers of CNA events. Using this information and the observed copy numbers of all genes along the chromosome, we construct AI models that predict the expected gene copy number for every gene. Models are built separately for each chromosomal arm and tumor type. When applied to an analyzed cohort, the frequency of driver mutations is used to predict the expected copy number profile along chromosomes. Observed copy numbers are compared with expected rates to highlight genes and entire loci under positive selective pressure.

Detection of cohort-specific drivers

For point mutations and indels, the background mutation rate is known to correlate with sequence context and chromatin accessibility [Supek F, et al. DNA Repair 2019](#); [Polak P et al. Nature 2015](#). We utilize tumor-type-specific and pan-cancer maps of expected mutation rates generated by AI models trained on hundreds of epigenetic profiles and nucleotide composition patterns.

These maps enable precise calculation of mutation excess and depletion in any given cohort, facilitating the identification of tumorigenesis drivers [Sherman MA, et al. Nat Biotechnol. 2022](#). Genes that accumulate an excess of truncating mutations (e.g., stop-gain, frameshift, splice-site) are likely tumor suppressors

negatively selected during tumor evolution (e.g., TP53, SMAD4)—tumor cells disable the activity of these genes. Activating (gain-of-function) mutations accumulate at specific positions in oncogenes (e.g., G12C substitution in KRAS). In contrast to truncating mutations in suppressor genes, activating mutations are typically missense, but can also be non-coding (e.g., TERT promoter) or result from gene fusion events.

Maps of expected rates of small variants enable precise attribution of mutational pressure to genes and other functional DNA elements (promoters, enhancers), proving highly effective in identifying drivers. However, for the majority of genes, background mutation rates are too low to robustly demonstrate depletion of mutations. In these cases, copy number changes, including partial losses and shallow amplifications, provide valuable complementary information.

AI model for biomarker identification

Susceptibility to inhibition of the gene of interest (GoI) is assessed by measuring enrichment in GoI amplifications (indicating likely dependence on elevated GoI protein levels) and GoI retention (depletion in GoI losses). To evaluate the relationship between biomarkers and GoI amplifications and deletions, tumors are stratified into thousands of categories based on biomarker mutation status (e.g., bi-allelic gene loss, mono-allelic gene loss, amplification, or activation) and compared to non-mutated controls.

For each biomarker-GoI alteration pair, a logistic regression model is constructed to predict GoI amplification (and GoI retention) based on two predictors: biomarker status and a confounding variable—the overall rate of amplifications (or partial losses) in the tumor. This analysis is performed both pan-cancer and within individual tissue types. P-values and odds ratios (ORs) are used to prioritize candidate biomarkers.

The technological details of the presented technology are part of Gordion IP and are not publicly available.

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