Moving towards personalized care

ICCC

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Precision medicine and chordoma

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Outline

- What is precision medicine and how does it work?
- Types of genomic profiling tests
- Practical considerations for chordoma patients
- How is research advancing the outlook for precision medicine in chordoma?

What is personalized or “precision” medicine?

- Match the right patient with the right drug
- Considers the **molecular profile** of cancers to be of key importance, rather than their tissue of origin
- Typically utilizes **genomic profiling** to identify biomarkers for targeted therapy or immunotherapy

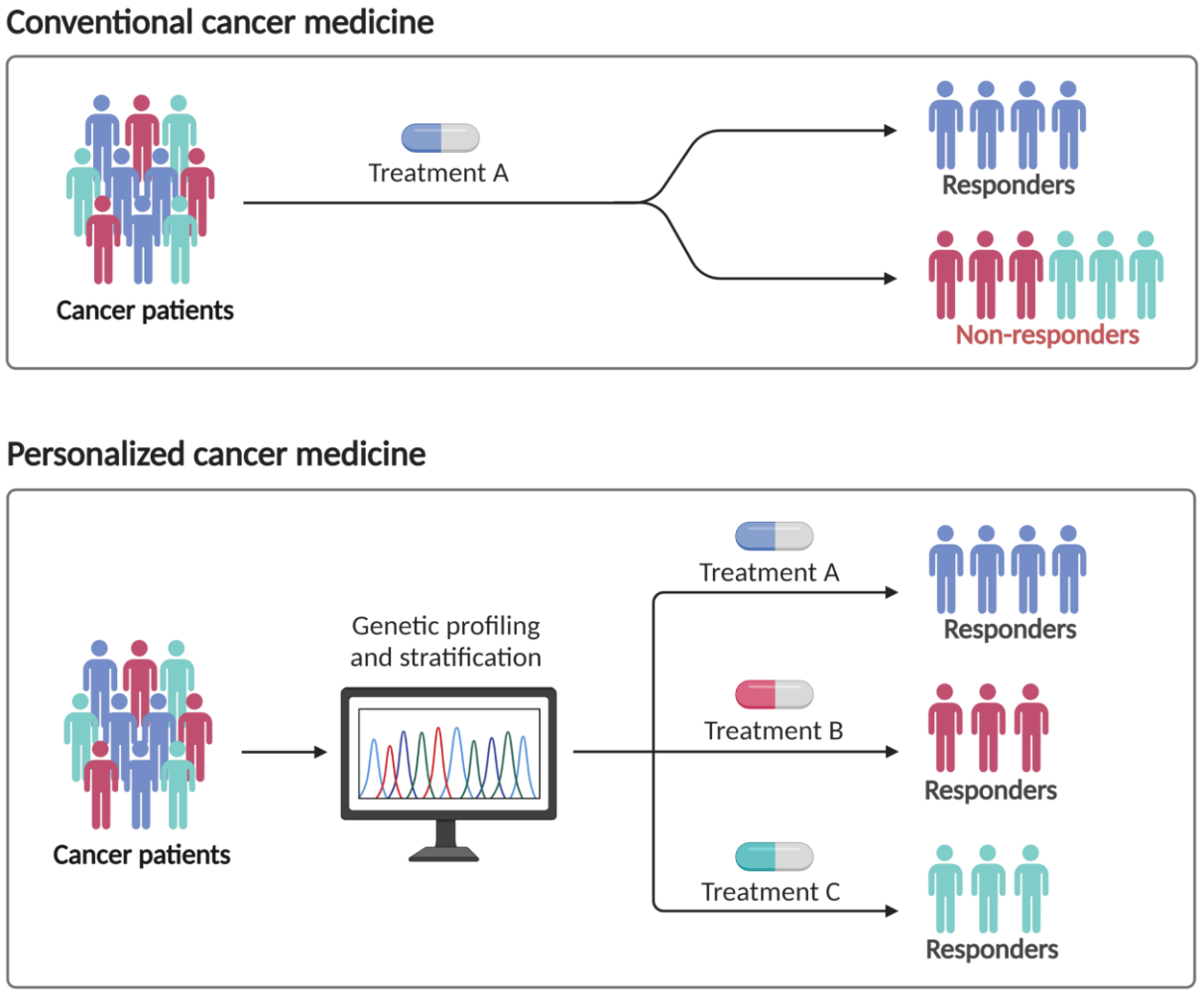
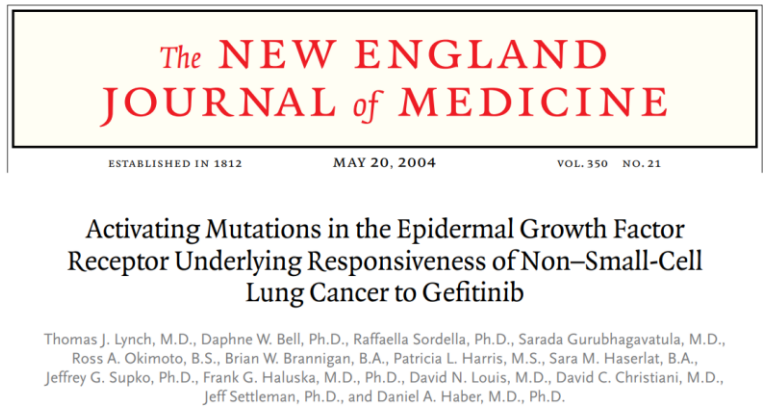


Figure created with BioRender.com

Precision oncology: birth of the “magic bullet” era



1998
Trastuzumab (Herceptin®) approved for HER2+ breast cancer

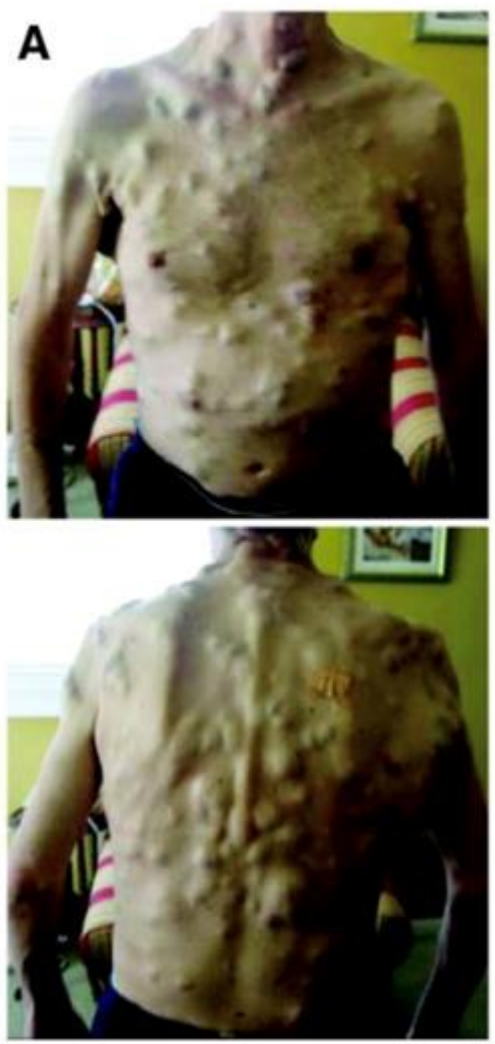
2001
Imatinib (Gleevec®) approved for CML with BCR-ABL gene fusion

2004
Gefitinib (Iressa®) approved for EGFR-mutated lung cancer

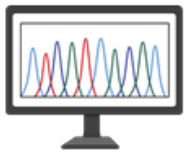
*Established a new paradigm focused on understanding the range of **DNA mutations** responsible for cancer growth, and developing drugs targeted against each mutation*

The promise of precision oncology

38-yo metastatic melanoma patient

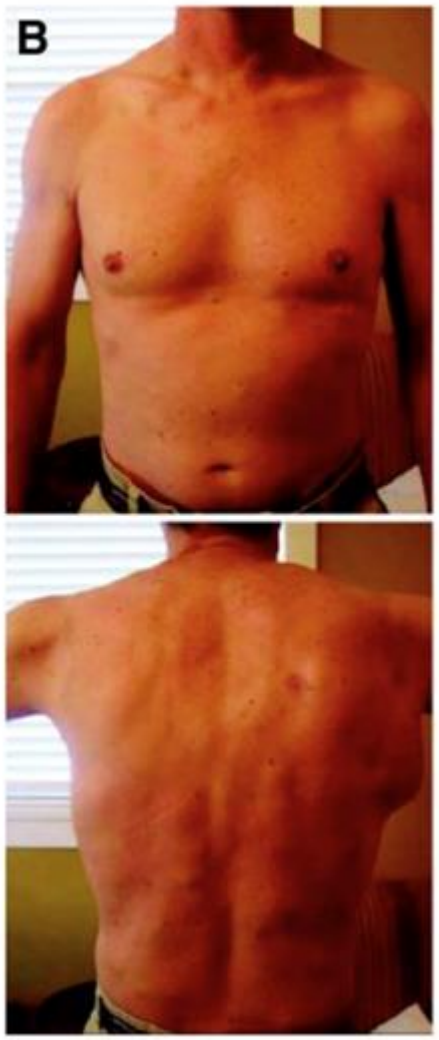


Genetic profiling



Oncogenic BRAF mutation detected

BRAF inhibitor



Adapted from Wagle et al., J Clin Oncol, 2011

2010s: Genomics-guided precision oncology comes of age

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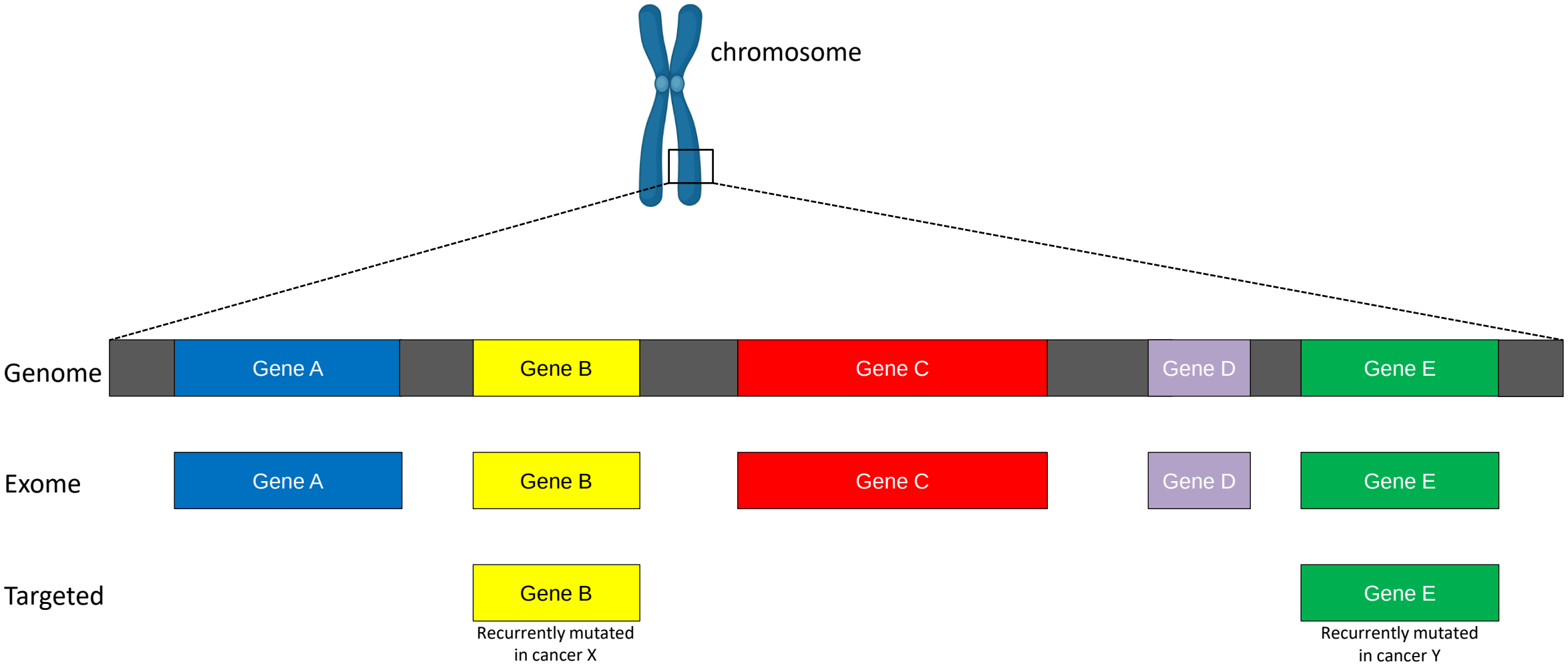
Approaches to DNA (genomic) profiling



Comparison of genomic profiling approaches

	Targeted	Whole-exome	Whole-genome
Coverage (breadth)	~500 genes analyzed	~20,000 genes analyzed	Full genome
Turnaround time	~2 weeks	~2 weeks	weeks to months
Sensitivity	Very high	High	Decent

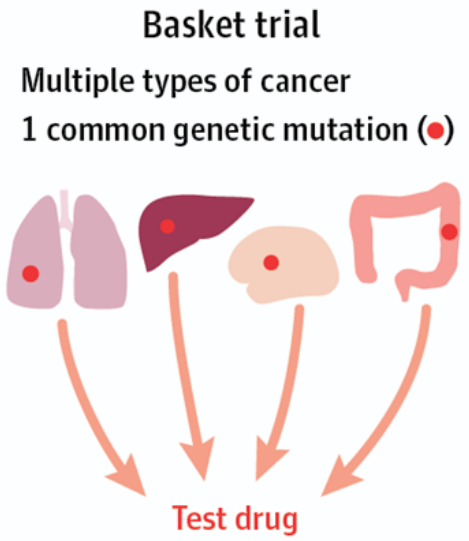
- Targeted profiling panels are ***limited*** and ***biased*** in their gene coverage, and are typically optimized for a few common cancer types
- Due to differences in disease biology, targeted panels can miss potentially actionable mutations
- **Whole-exome** profiling provides more information, and has become increasingly economical and practical in recent years

Practical considerations for chordoma patients

1. Who should consider tumor profiling?
   - Chordoma patients in need of systemic therapy should consider whether testing is right for them
   - Discussing the pros and cons with your oncologist can help you make the best decision for your individual situation
   - New or archival tumor samples can be used (surgery, biopsy)

Practical considerations for chordoma patients

2. Are test results needed for enrollment in clinical trials?
   - Circumstantial – it depends on the trial (check eligibility criteria)
   - Results can help point to personalized clinical trial, off-label, or compassionate use opportunities
   - Precision oncology trials: NCI-MATCH, TAPUR
   - “Basket” trials

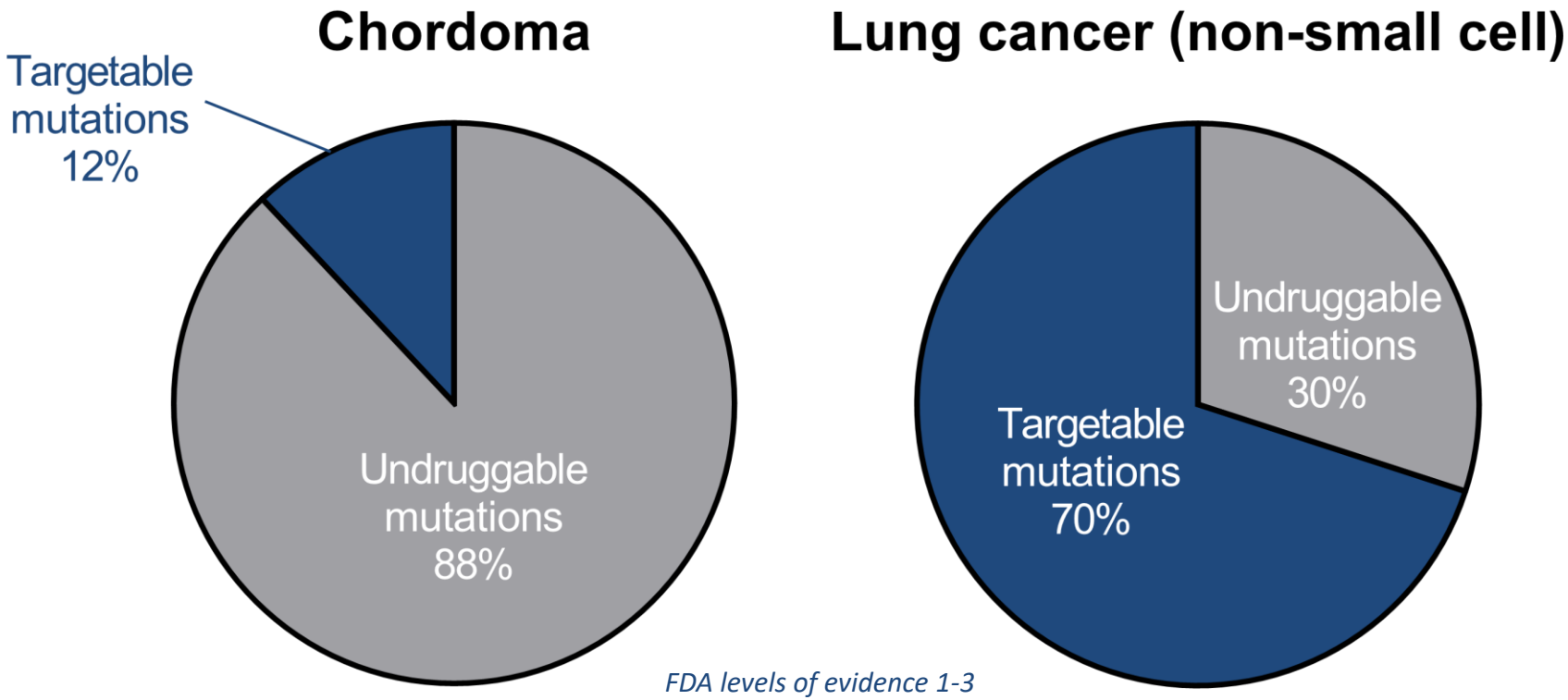


H West, JAMA Oncol, 2017

Practical considerations for chordoma patients

3. Are the test results guaranteed to identify a biomarker for personalized therapy?
   - Oftentimes no currently-actionable mutations are found
   - Actionable mutations but inaccessible therapies (e.g. ineligibility for clinical trial)
   - What works for some people doesn't work for others (i.e. response rate < 100%)

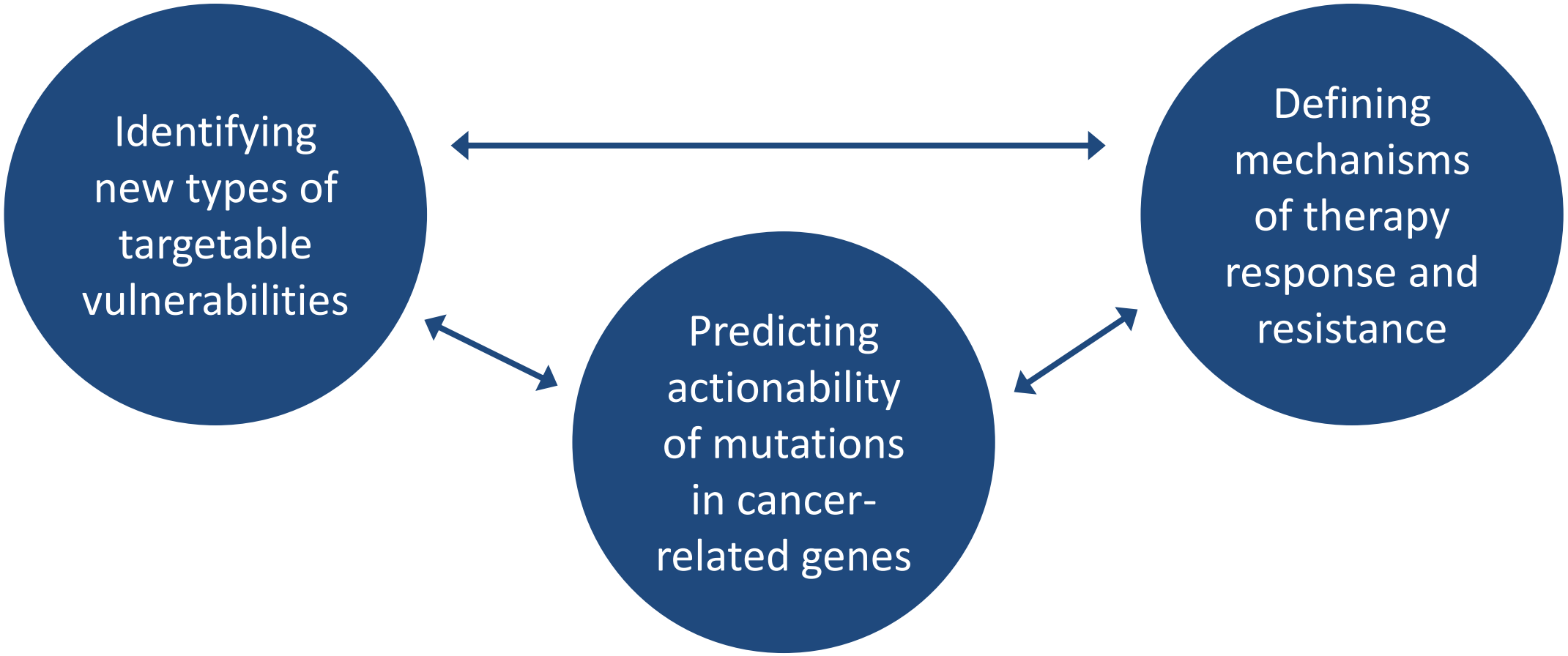
Most chordoma patients have not benefitted from genomics-guided precision oncology



FDA levels of evidence 1-3
AMP/ASCO/CAP levels A-C
FDA-approved or investigational therapies for specific alteration in any cancer type

How can research maximize the number of chordoma patients that benefit from personalized medicine?

Grow our understanding of chordoma biology through:



Predicting the actionability of mutations in cancer-related genes

- Through the lens of current genomic profiling tests, well-validated therapeutic biomarkers are rare in chordoma
- In the absence of recognized biomarkers, **potentially actionable alterations** or **variants of unknown significance (VUS)** in cancer-related genes can suggest possible therapeutic opportunities based on **emerging science**
- These are typically listed near the end of the report and should be discussed with your oncologist

SOMATIC VARIANT DETAILS - POTENTIALLY ACTIONABLE

TP53 c.586C>T p.R196* NM_000546 Stop gain - LOF VAF: 61.4%

TP53 encodes a tumor suppressor that is commonly disabled across cancer types. It normally functions to activate cellular DNA repair mechanisms, plays a role in cell cycle progression in response to DNA damage, and can initiate apoptosis. Loss of function mutations, copy number loss, and epigenetic modifications resulting in underexpression of TP53 are associated with cancer progression.

AR Copy number gain

AR encodes the androgen receptor protein, a hormone receptor important for male sexual development during embryonic development and again at puberty. Binding of androgens, such as testosterone, results in an androgen-receptor complex that binds to DNA and regulates the activity of androgen-responsive genes. Activating mutations and copy number gains of AR are associated with cancer progression.

CDKN2A Copy number loss

CDKN2A encodes two proteins, p16(INK4a) and p14(ARF), that function in regulating cell growth. The p16(INK4a) protein regulates the cell cycle through the inhibition of CDK4 and CDK6, preventing them from stimulating cell proliferation. The p14(ARF) protein binds to MDM2 to keep p53 intact and stimulate the p53-dependent cell cycle arrest and apoptosis. Loss of function mutations, copy number loss, and underexpression of CDKN2A are associated with cancer progression.

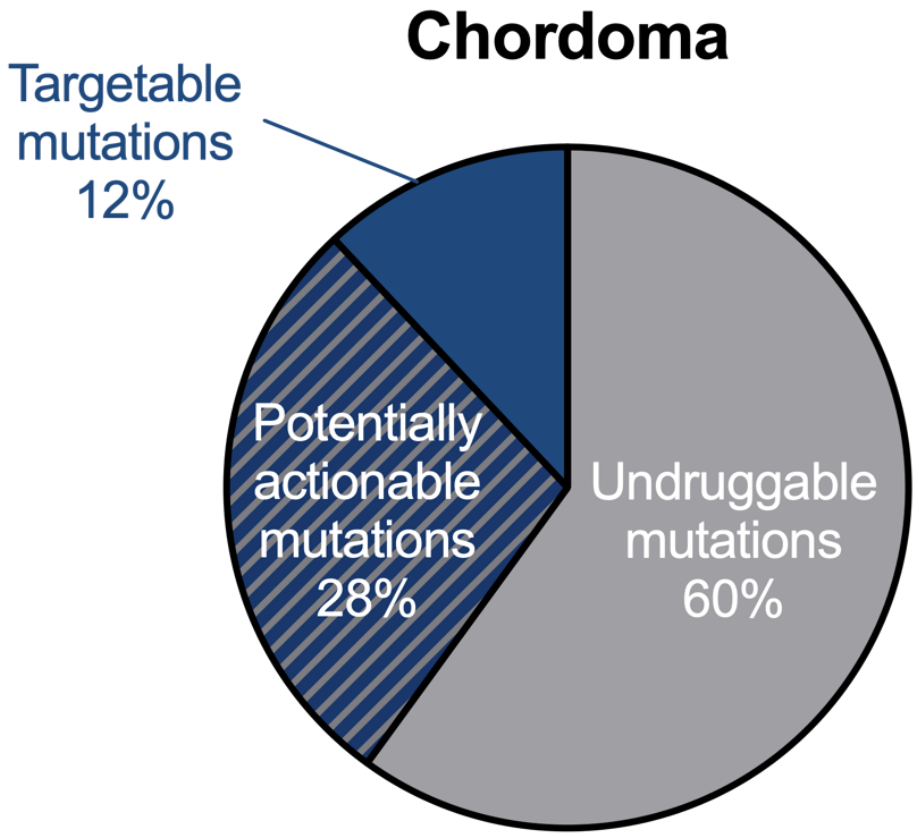
TMPRSS2 - ERG Chromosomal rearrangement

ERG is an oncogene and transcription factor in the erythroblast transformation-specific (ETS) family. It normally functions in embryonic development, cell differentiation, apoptosis, and angiogenesis. ERG forms an oncogenic fusion gene with the 5'-UTR of TMPRSS2. The 5'-UTR of TMPRSS2 contains androgen responsive regulatory elements that drive ERG overexpression. In addition to this fusion, amplification and overexpression of ERG are associated with cancer progression.

VARIANTS OF UNKNOWN SIGNIFICANCE

Somatic	Mutation effect	Variant allele fraction
TMPRSS2	c.1339_1424del p.C447fs Frameshift NM_001135099	38.0%
EGF	c.1153G>C p.G385R Missense variant NM_001963	37.3%
FGFR4	c.2273G>A p.R758H Missense variant NM_002011	33.3%
FGFR4	c.1985T>C p.F662S Missense variant NM_002011	29.4%
BCL11B	c.2098G>A p.A700T Missense variant NM_138576	26.5%

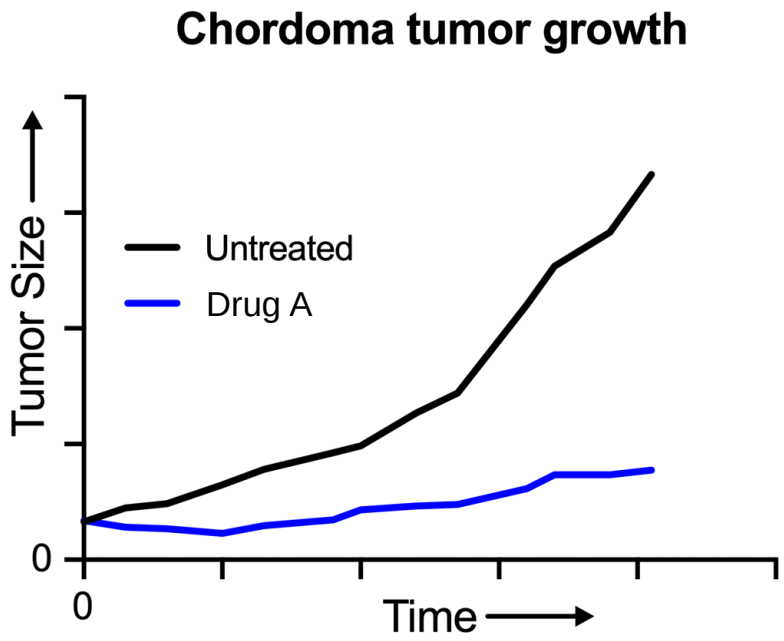
Predicting the actionability of mutations in cancer-related genes

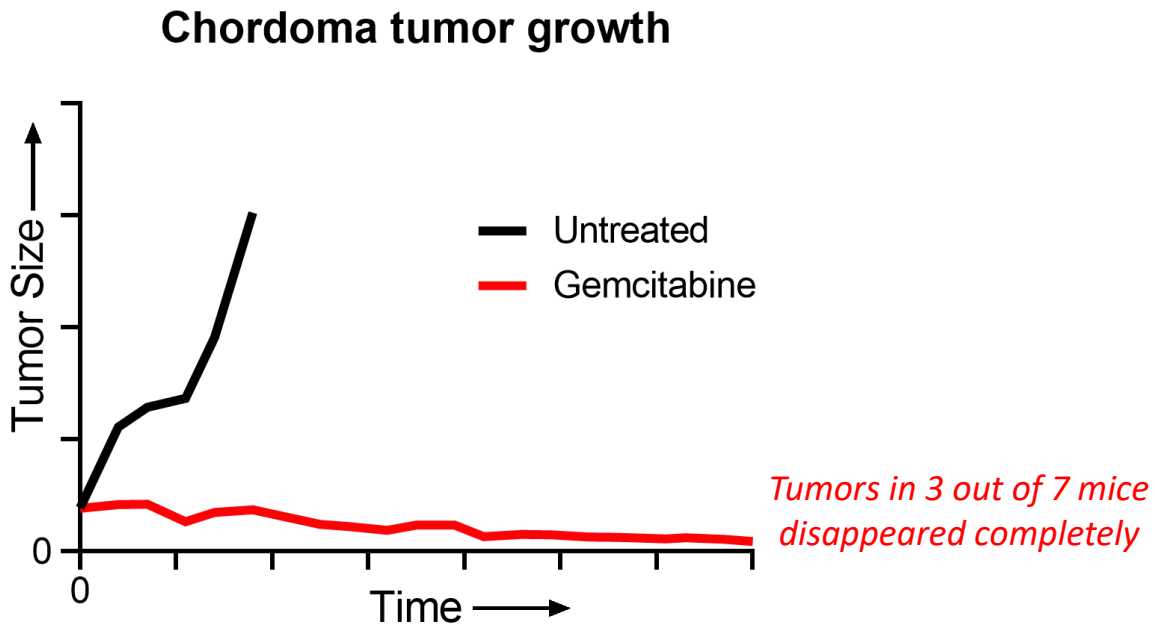


Now up to 40% of patients may benefit from genomics-guided precision oncology

when including reported actionable mutations + potentially actionable/VUS in cancer-related genes

SMARCB1/INI1 mutations create a targetable Achilles' heel

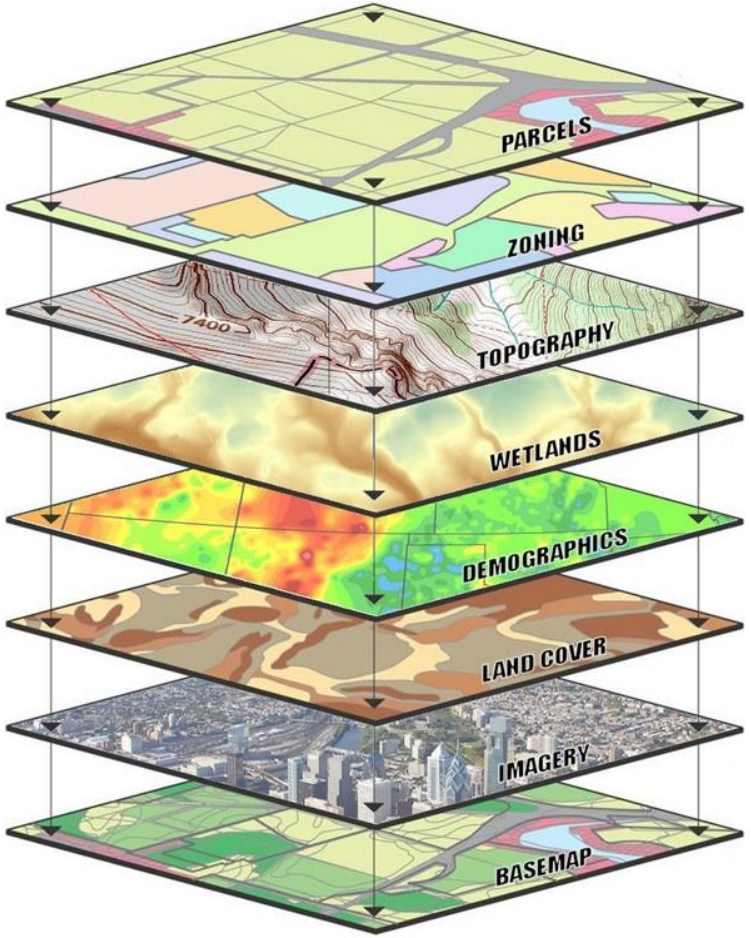




- Drug Screening Program collaboration with Dr. Greg Cote at MGH identified vulnerability created by mutations in SMARCB1/INI1 gene
- Important to repeat this experiment in more chordoma models, plus complementary experiments in our new lab
- Extending these observations to related genes to understand if more chordoma patients could benefit

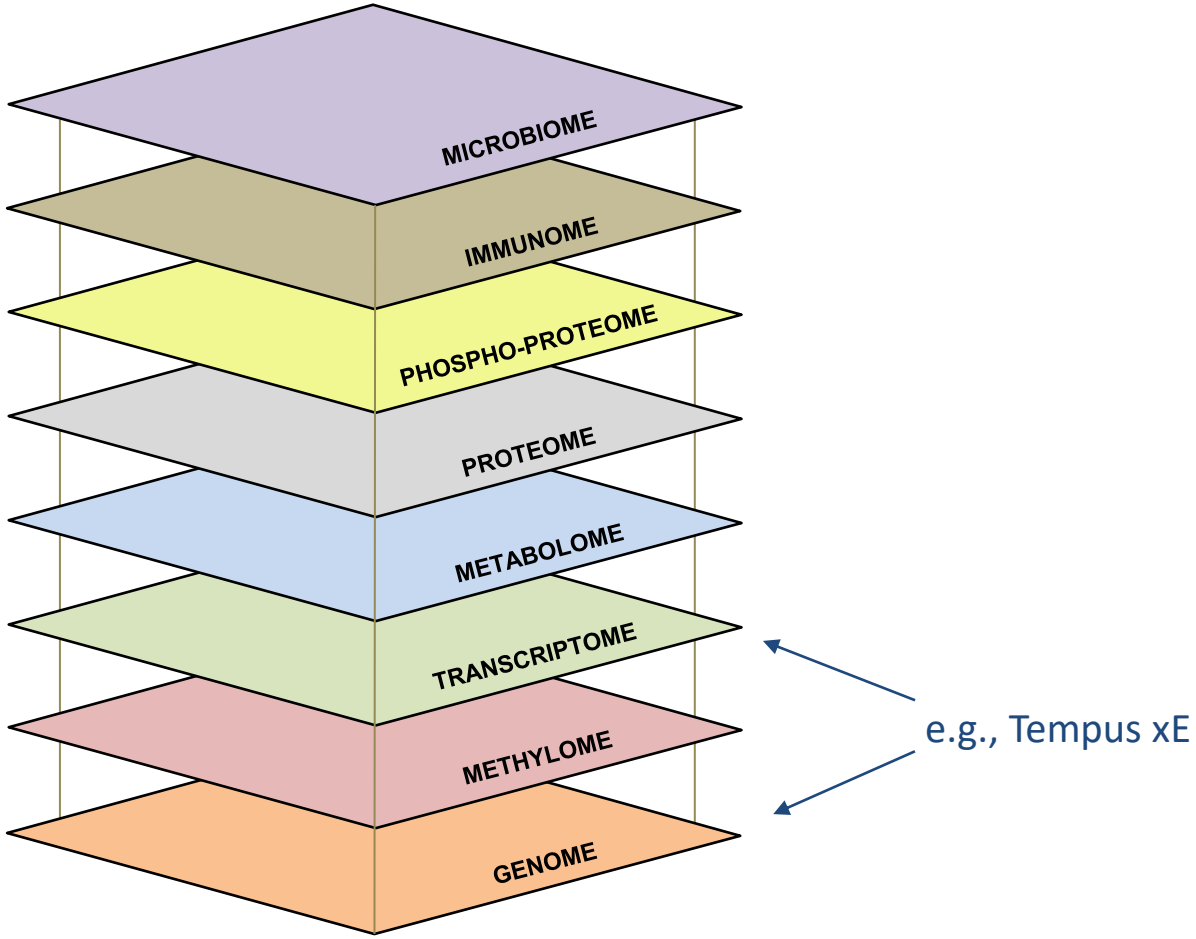
Multiple integrated systems contribute to tumor biology

Geography



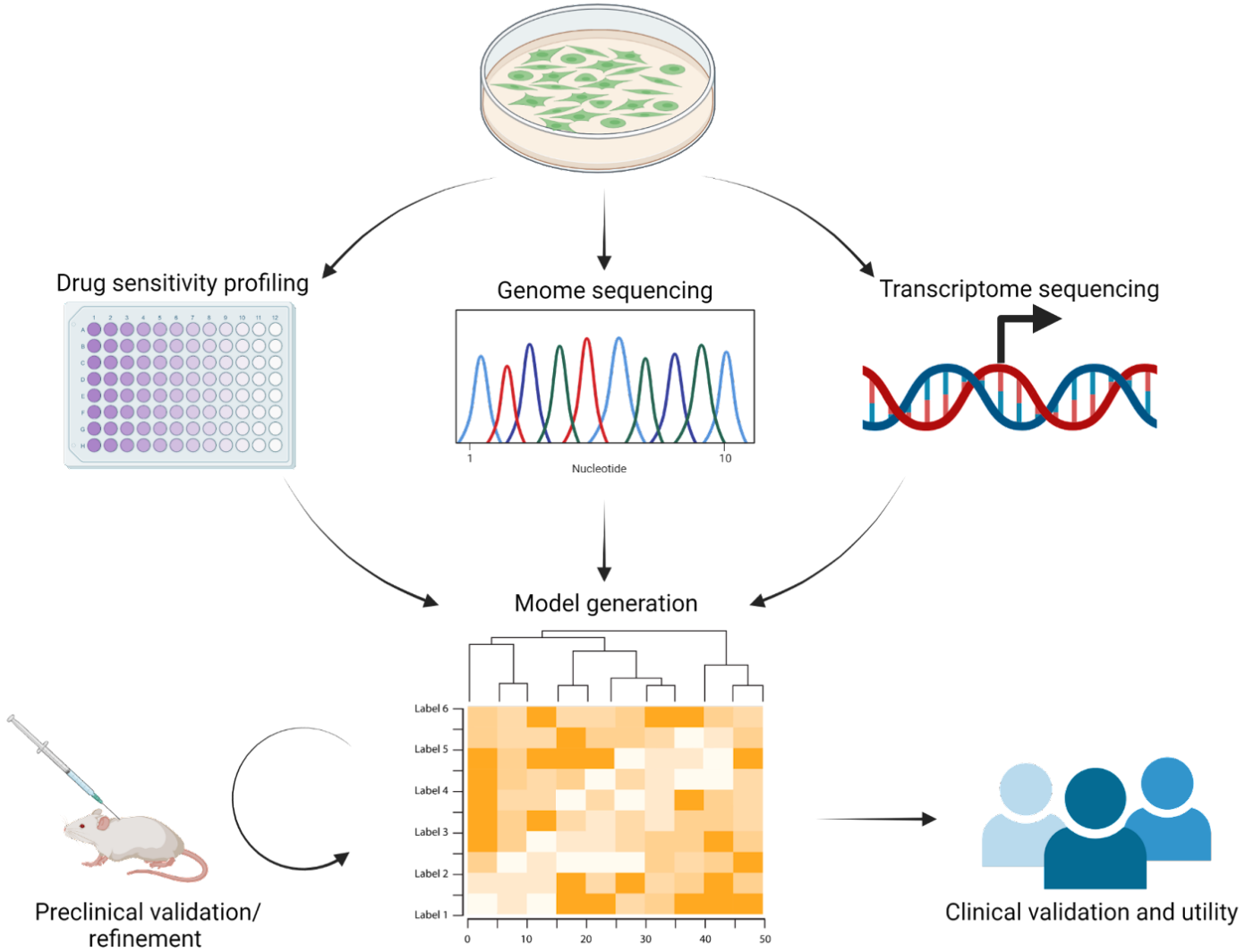
Source: usgs.gov

Biology



Opportunities for personalized medicine exist within each layer; combining more layers provides fuller picture

Identifying responders to EGFR inhibitors



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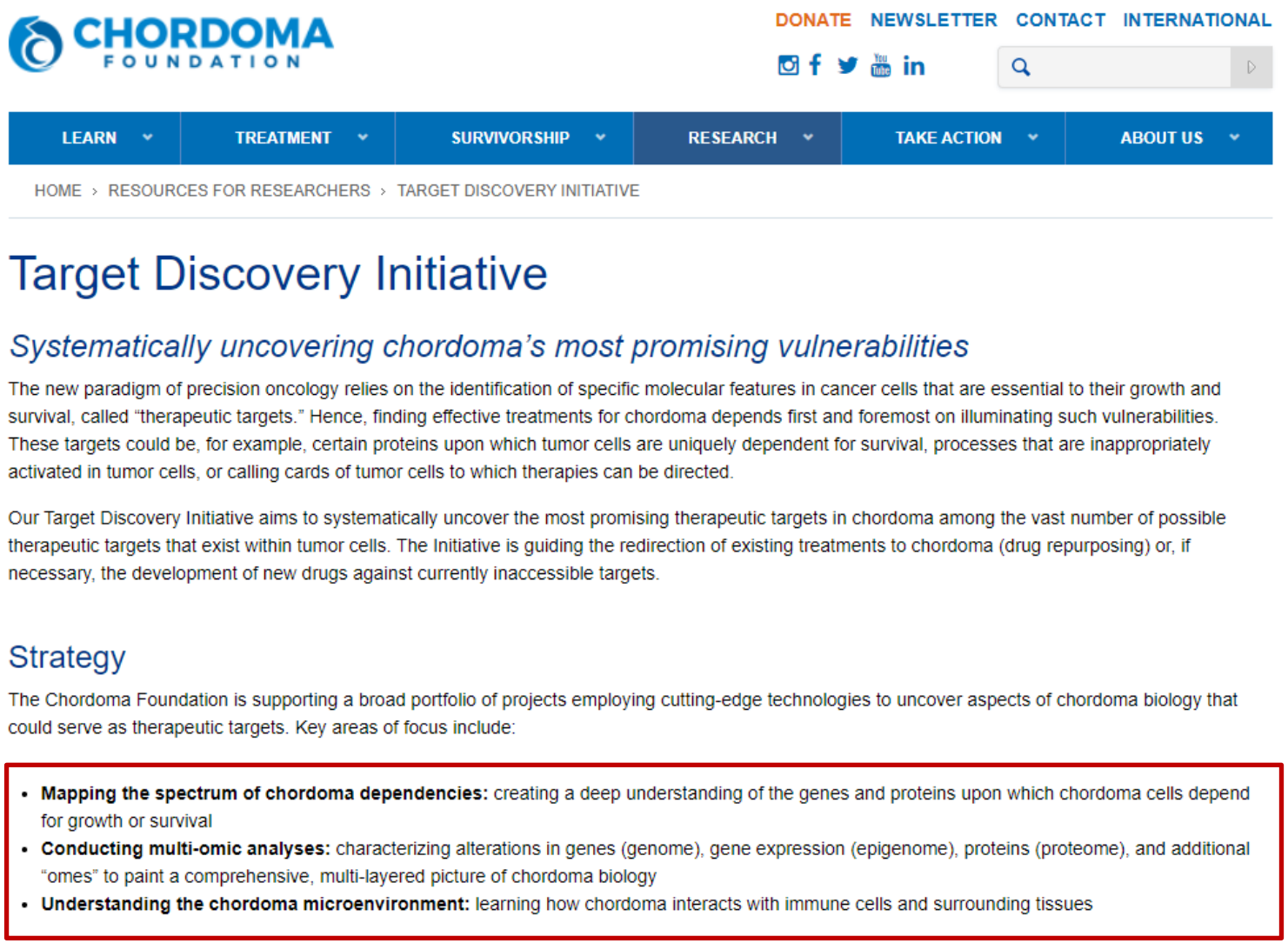
Identifying and validating new types of therapeutic vulnerabilities



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Target Discovery Initiative

Systematically uncovering chordoma's most promising vulnerabilities

The new paradigm of precision oncology relies on the identification of specific molecular features in cancer cells that are essential to their growth and survival, called "therapeutic targets." Hence, finding effective treatments for chordoma depends first and foremost on illuminating such vulnerabilities. These targets could be, for example, certain proteins upon which tumor cells are uniquely dependent for survival, processes that are inappropriately activated in tumor cells, or calling cards of tumor cells to which therapies can be directed.

Our Target Discovery Initiative aims to systematically uncover the most promising therapeutic targets in chordoma among the vast number of possible therapeutic targets that exist within tumor cells. The Initiative is guiding the redirection of existing treatments to chordoma (drug repurposing) or, if necessary, the development of new drugs against currently inaccessible targets.

Strategy

The Chordoma Foundation is supporting a broad portfolio of projects employing cutting-edge technologies to uncover aspects of chordoma biology that could serve as therapeutic targets. Key areas of focus include:

- **Mapping the spectrum of chordoma dependencies:** creating a deep understanding of the genes and proteins upon which chordoma cells depend for growth or survival
- **Conducting multi-omic analyses:** characterizing alterations in genes (genome), gene expression (epigenome), proteins (proteome), and additional "omes" to paint a comprehensive, multi-layered picture of chordoma biology
- **Understanding the chordoma microenvironment:** learning how chordoma interacts with immune cells and surrounding tissues

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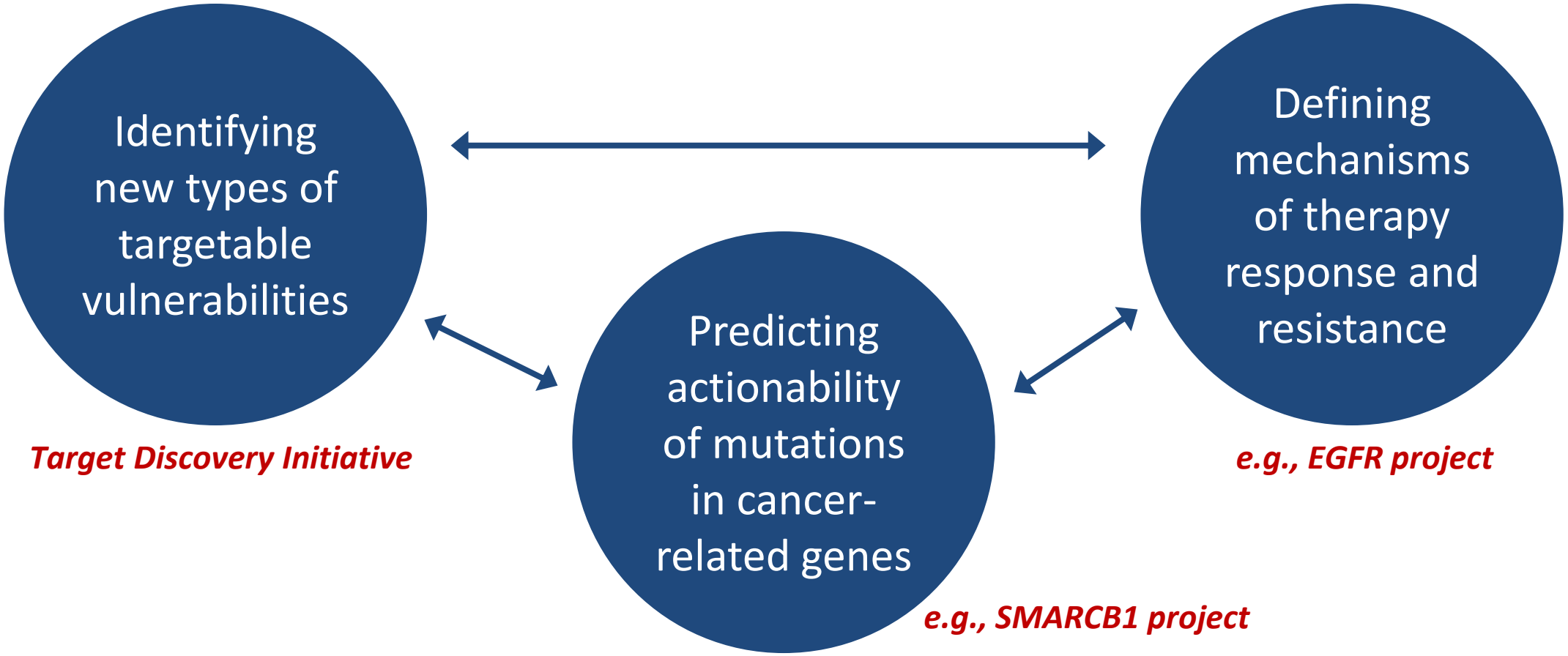

Thank you

Questions?