A New Prescription: Genomic-Driven Oncology for the Forward-Thinking Pharmacist

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Disclosures

I have no actual or relevant financial relationships to create a potential conflict of interest in relation to the content of this presentation

Acknowledgements

- Mary Walters, PharmD, BCOP
- Ryan Nguyen, DO

Abbreviations

ASCO – American Society of Clinical Oncology

CADs – cancer access data shelter

CNV – copy number variant

CPIC - Clinical Pharmacogenetics Implementation Consortium

FISH – Fluorescence in situ hybridization

GWAS - genome-wide association studies

IHC - Immunohistochemistry

MTB – Molecular Tumor Board

mBCa – Metastatic Breast Cancer

NGS – Next Generation Sequencing

POTB – Precision Oncology Tumor Board

PCR – polymerase chain reaction

PD – Pharmacodynamics

PK - Pharmacokinetics

PM – Precision Medicine

POTB – Precision Oncology Tumor Board

RWD – Real World Data

TNBC – Triple Negative Breast Cancer

VUS – variant of uncertain significance

WES – Whole Exome Sequencing

WGS – Whole Genome Sequencing

Objectives

01 Define the key terminologies associated with precision medicine in oncology

02 Describe the use of genomics in personalizing cancer treatment

03 Explore the benefits and challenges of integrating precision medicine into the pharmacy oncology practice

04 Identify recent advancements in genomic-driven oncology.

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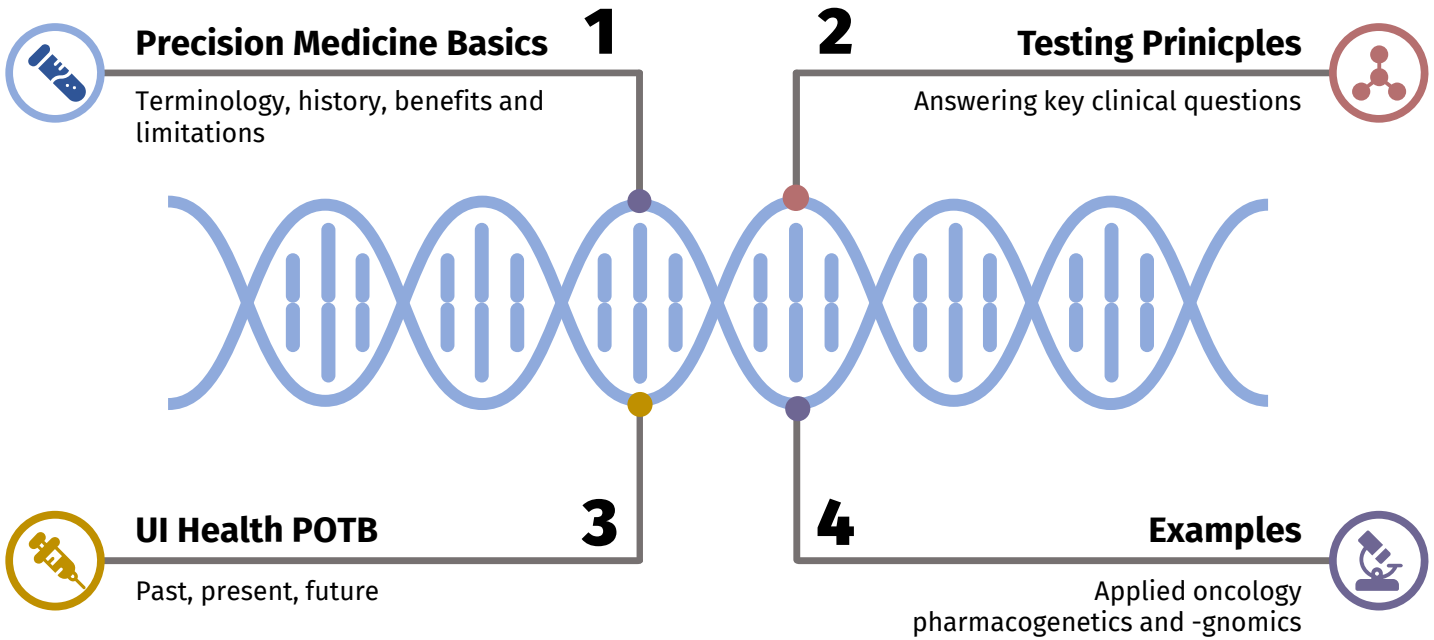
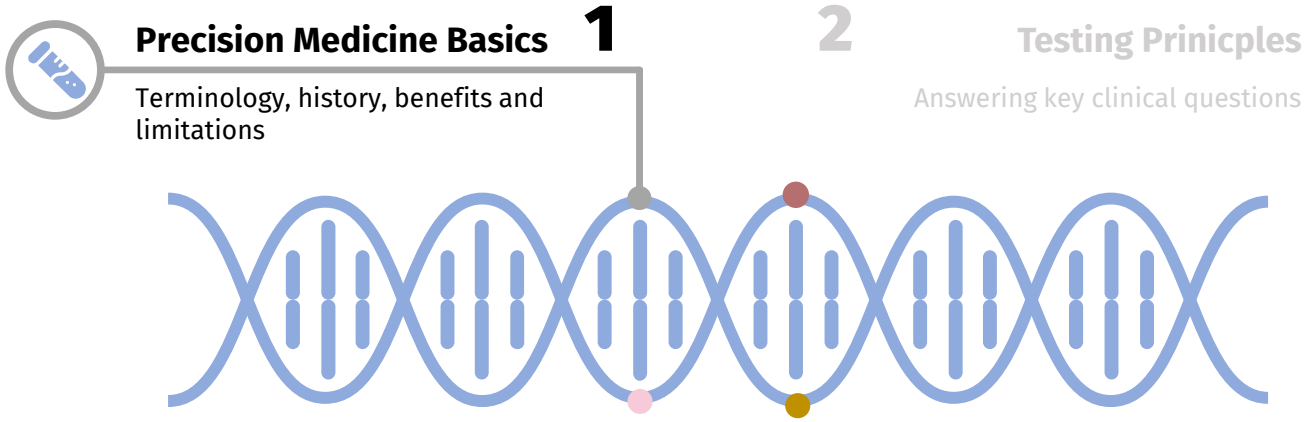
Outline


1
Precision Medicine Basics
Terminology, history, benefits and limitations
2
Testing Prinicples
Answering key clinical questions
3
UI Health POTB
Past, present, future
4
Examples
Applied oncology pharmacogenetics and -gnomics

Outline



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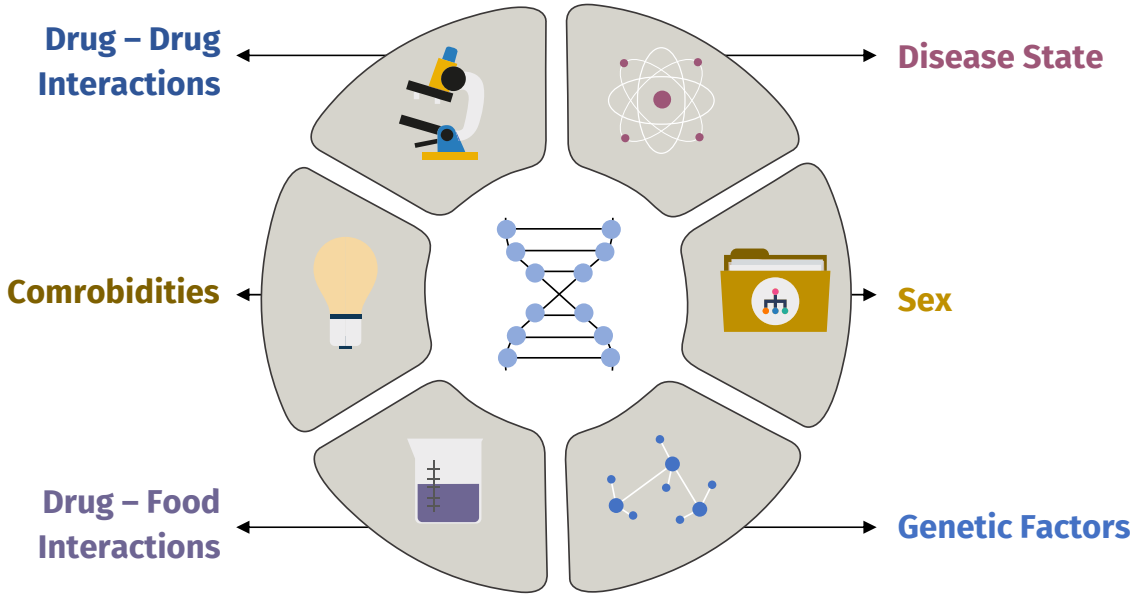
Precision Medicine

Tremendous interindividual variability in the response to pharmacologic agents



Application of patient-specific clinical and genetic/genomic profiles to decisions regarding prevention, diagnosis, and treatment of disease

Eur J Pharmacol. 2000 Dec 27;410(2-3):121-130.
JAMA. 1997 Jan 22-29;277(4):301-6.
J Intern Med. 2001 Sep;250(3):186-200

General Terminology

- **Pharmacogenomics** = role of various components of the genome on pharmacokinetic and –dynamic activity of a drug
    - **Pharmacogenetics =** refers to the role of a specific DNA polymorphism or coding variant effects drug response

PK	PD
Absorption	Drug targets
Distribution	Enzymes
Metabolism	Receptors
Excretion	Ion Channels
	Transporters
	Immune System

J Psychiatr Pract. 2013 Mar;19(2):142-9.

Slide credit: Adapted from Walters, M, OPM CUW, 2022.

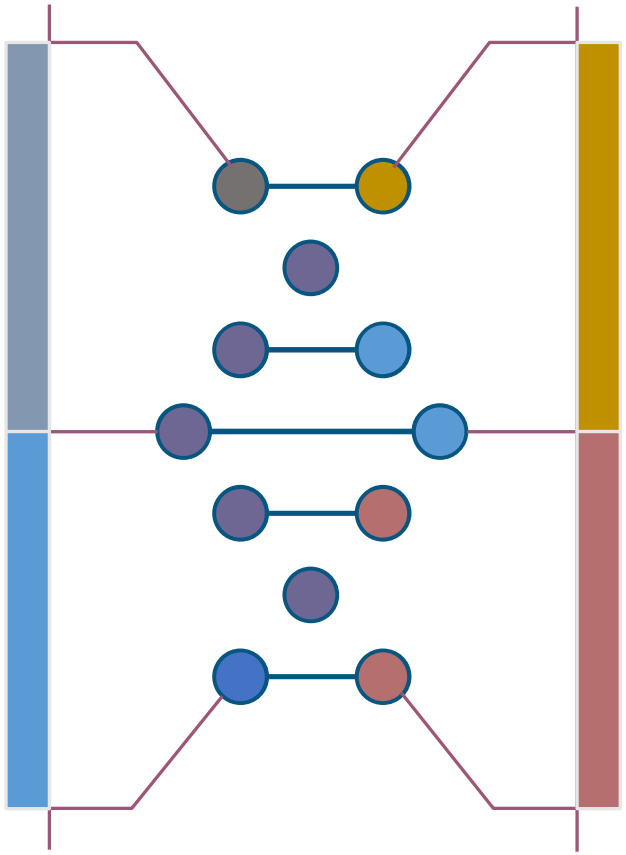
General Terminology

Germline

- Hereditary mutations found in germ cells. Affects all cells within the body
- Passed down through generations
- Influences risk for developing disease

Genotyping

- Determining the combination of alleles (variants) at a specific location in the genome



Somatic

- Occur in non-reproductive cells (i.e tumor)
- Cannot be inherited, but accumulate
- May impart growth advantage (driver) or have no clinical effect (passenger)

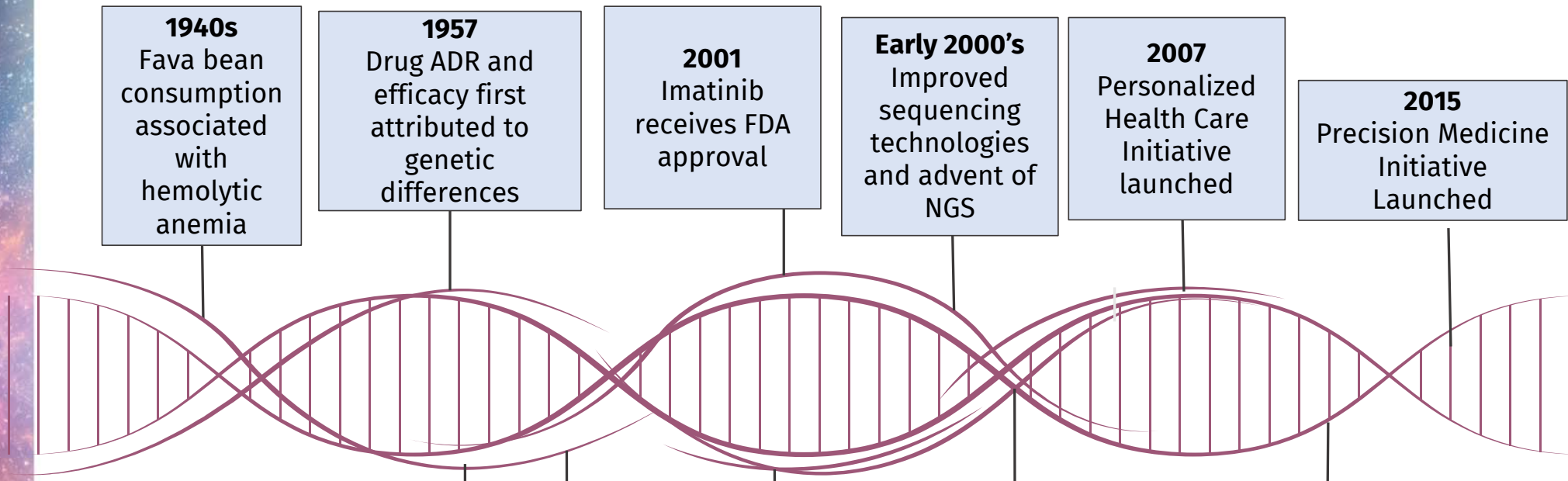
Genetic variation

- Differences in genetic sequences among individuals in a population

Eur J Pharmacol. 2000 Dec 27;410(2-3):121-130

Slide credit: Adapted from Walters, M, OPM CUW, 2022.

History of Precision Medicine



6th Centry BC – Varation in fava bean tolerability observed

1940s Fava bean consumption associated with hemolytic anemia

1957 Drug ADR and efficacy first attributed to genetic differences

1959 "Pharmagenetics" first coined

1970s First example of applied genotyping

2001 Imatinib receives FDA approval

1998 Trastuzumab FDA approved for HER2+ mBCa

Early 2000's Improved sequencing technologies and advent of NGS

2000's - present multiple driver mutations and targeted therapies discovered in NSCLC

2007 Personalized Health Care Initiative launched

2008 Genetic Information Nondiscrimination Act (GINA) passed

2015 Precision Medicine Initiative Launched

- *Pharmacogenomics, PDQ Medical Genetics (Ed), Elsevier, Oxford 2002. p.232.*
- Precision Oncology: Who, How, What, When, and When Not?. *Am Soc Clin Oncol Educ Book* **37**, 160-169(2017).

Slide credit: Adapted from Walters, M, OPM CUW, 2022.

Potential Benefits

Non-Molecular Directed

- With each line of therapy duration of sequential chemotherapy generally **LESS** effective compared to prior therapy

$$\frac{\text{Duration of PFS (Second line Chemo)}}{\text{Duration of PFS (First line Chemo)}} \leq 0.8$$

Molecular Directed

- With each line of therapy duration of sequential therapy generally **MORE** effective compared to prior therapy

$$\frac{\text{Duration of PFS (Molecular)}}{\text{Duration of PFS (first line Chemo)}} \geq 1.3$$

Radovich M. et al. (2016). Oncotarget, 7, 56491-56500.

Slide credit: Adapted from Walters, M, OPM CUW, 2022.

Guideline Recommendations

Various oncology societies recommend the use NGS and molecular profiling to guide treatment decisions, identify actionable genetic alterations, and support personalized cancer care across different types of cancer

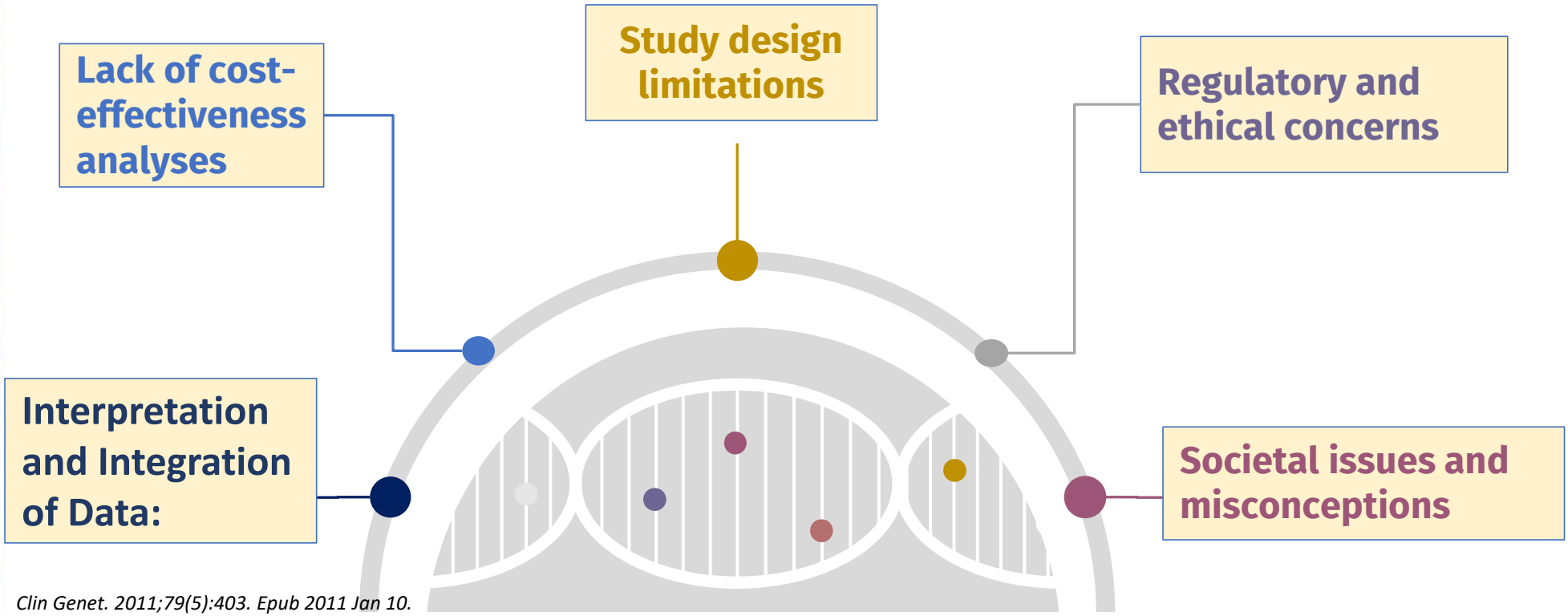
FDA-Approved Targeted Therapies in Oncology

ALK fusion	BRAF	BRCA1/BRCA 2	EGFR	EGFR exon 20	ERBB2 (HER2)
• Alectinib • Brigatinib • Ceritinib • Crizotinib • Lorlatinib	• Dabrafenib + trametinib • Encorafenib + binimetnib • Vemurafenib + cobimetinib	• Niraparib • Olaparib • Rucaparib • Talazoparib	• Afatinib • Dacomitinib • Erlotinib • Gefitinib • Osimertinib	• Amivantamab	•Ado-trastuzumab emtansine •Lapatinib •Margetuximab •Neratinib •Pertuzumab •Trastuzumab •Trastuzumab deruxtecan

EZH2	FGFR2/3 fusions	FLT3	IDH1	IDH2	KIT	KRAS G12C	MET
• Tazemetostat	• Erdafitinib • Infigratnib • Pemigatinib	• Midostaurin • Gilteritinib	• Ivosidenib	• Enasidenib	• Imatinib • Regorafenbi • Sunitinib	• Sotorasib • Adagrasib	• Cabozantinib • Capmatinib • Crizotinib • Tepotinib

NF1	PDGFRA	PIK3CA	RET fusion/mutation	ROS1 fusion	SMARCB1	MSI-H/TMB-H/dMMR/PD-L1
• Selumetinib • NTRK fusion • Entrectinib • Larotrectinib	• Avapritinib • Imatinib	• Alpelisib • Capivasertib	• Pralsetinib • Selpercatinib	• Crizotinib • Entrectinib • Repotrectinib	• Tazemetostat	• Immune Checkpoint Inhibitor

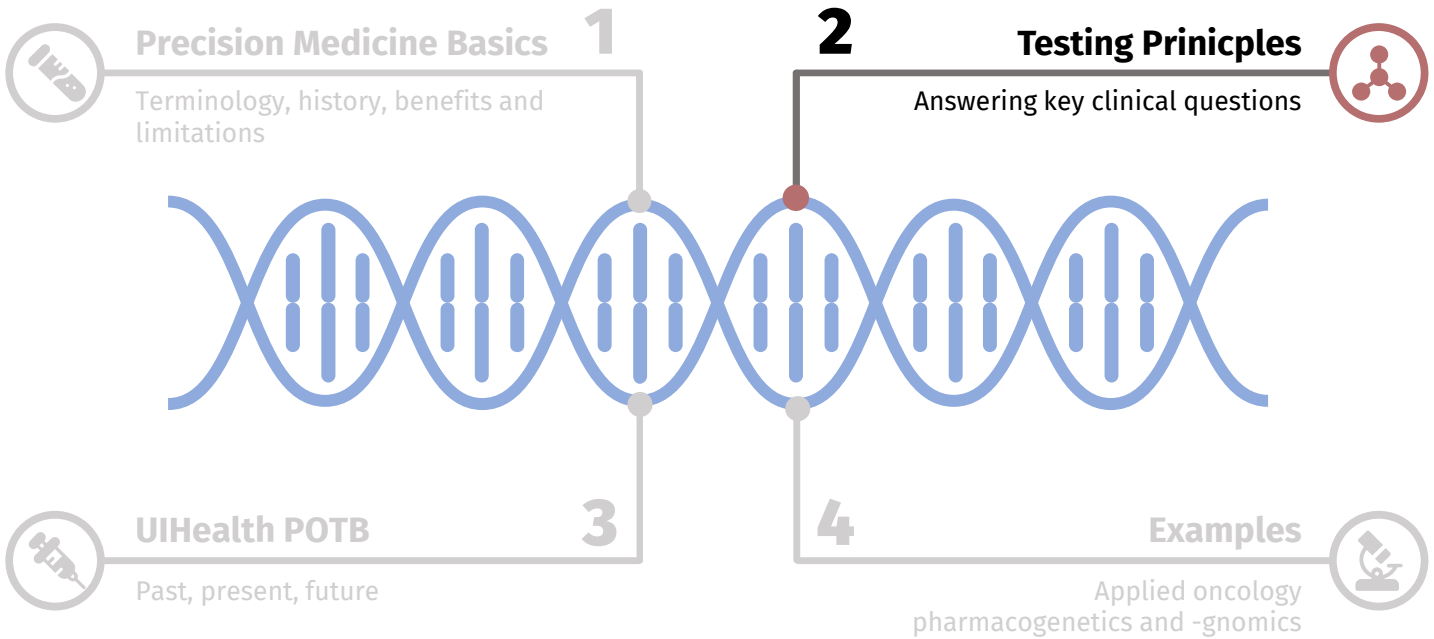
Current Limitations to Widespread Use



Clin Genet. 2011;79(5):403. Epub 2011 Jan 10.
P T. 2010;35(12):670.
Lancet. 2015 Apr;385(9978):1617.
N Engl J Med 2016; 375:1289-1294

Genet Med. 2011;13(1):63.
Lancet. 2010;375(9727):1749. Epub 2010 Apr 29.

Outline



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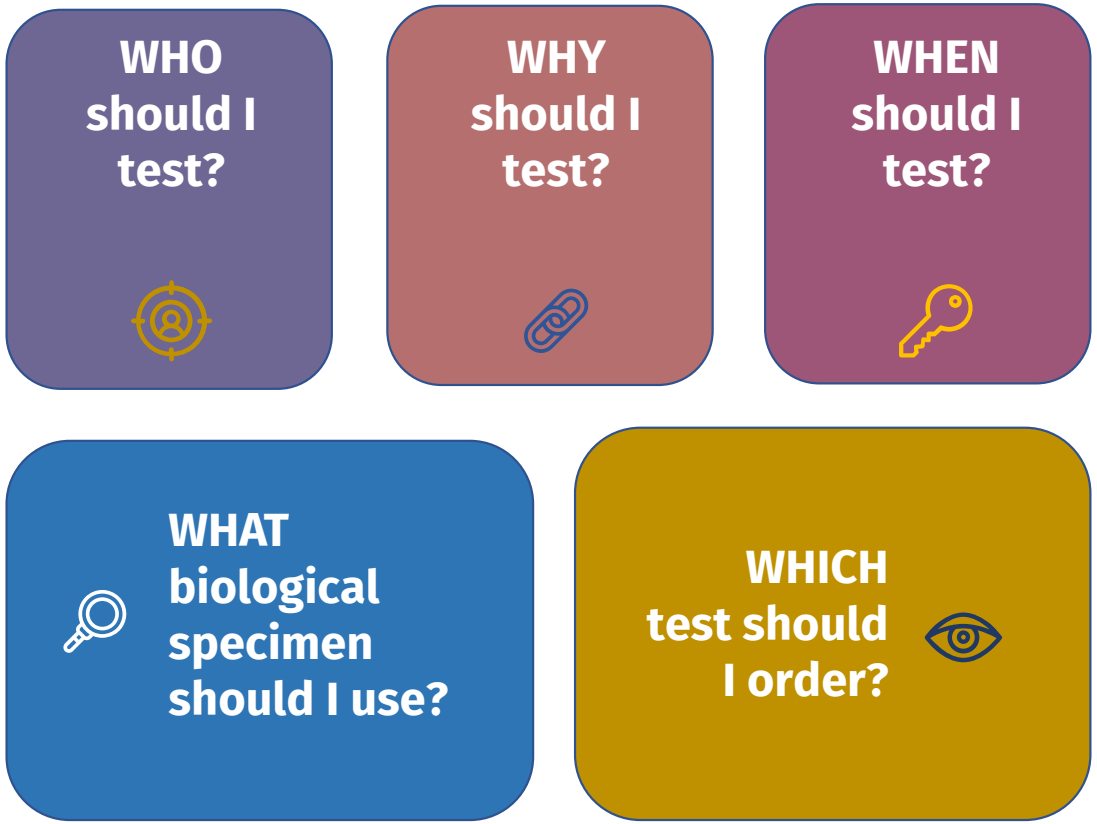
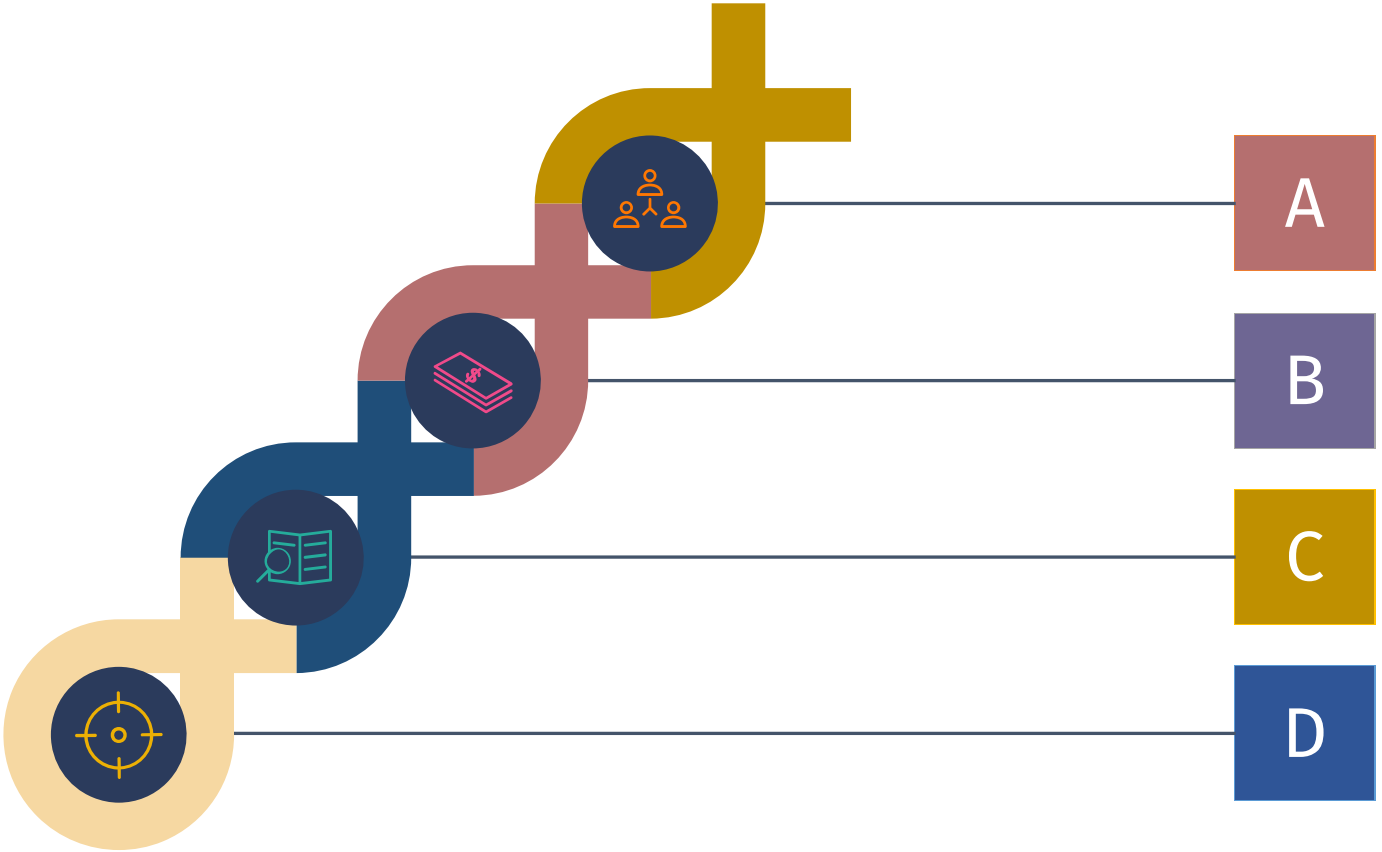
Key Clinical Questions

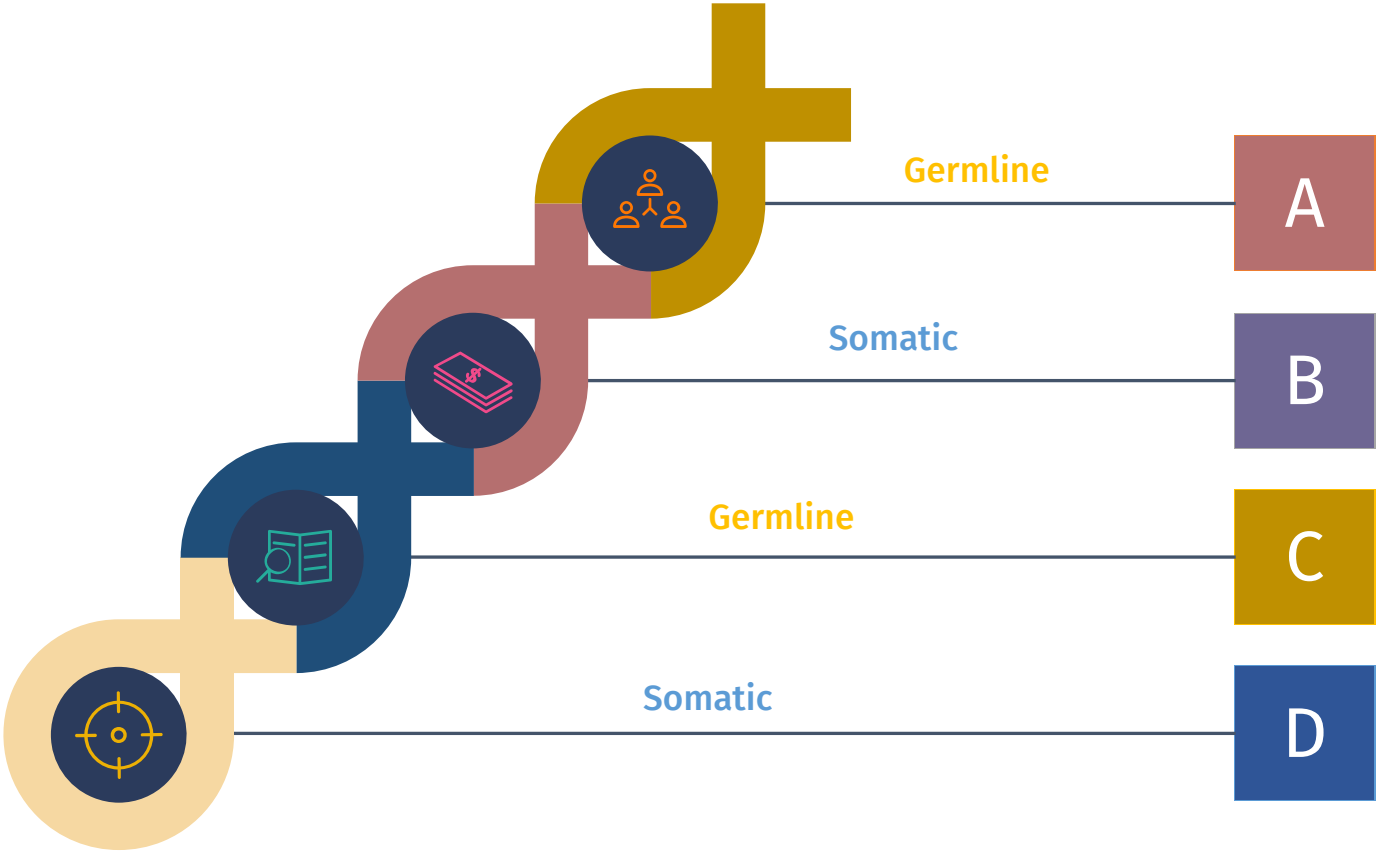


Clinical Application – Why test?



Slide credit: Adapted from Walters, M, OPM CUW, 2022.

Clinical Application – Who To Test?



Slide credit: Adapted from Walters, M, OPM CUW, 2022.

Extent of Testing – Which test?

Selected variants

Single-nucleotide genotyping panels
Genotype most common variants and hot spots first
Less expensive and faster turnaround time

Entire gene(s)

Sequences all nucleotides across the gene to ID pathogenic variants

- Single Gene
- Select Disease – Associated Set
- Comprehensive genome-wide

More expensive, longer turnaround time, complex interpretation and application

Copy number variation

Detection of deletions or duplications of exons or entire genes
Can be assessed on entire gene panels, IHC, FISH, but not single-nucleotide panels

Entire chromosome

Assessment of segmental chromosomal gains or losses, translocations, or other structural rearrangements
Not assessed on single-nucleotide panels

Slide credit: Adapted from Walters, M, OPM CUW, 2022.

Examples – Which test?

Selected variants

Somatic – uveal melanoma HLA-A*02:01 allele sequencing
Germline – factor V Leiden PCR

Entire gene(s)

Somatic
- Single gene: TNBC/ovarian BRCA1/2 sequencing
- Select Set: NGS Solid Tumor Mutation Panel
- Comprehensive: NGS Tumor molecular profiling

Germline
- Single gene: Hemophilia B sequencing
- Select Set: NGS Hereditary Cancer Syndrome Panels
- Comprehensive: Limited clinical use

Copy number variation

Somatic – HER2 + breast caner IHC→FISH
Germline – Trisomy 21 MDS cytogenetics

Entire chromosome

Somatic – CML/ALL t(9;22) aka BRC-ABL cytogenetics
Germline – Telomere flow cytometry-FISH

Nature. 1994 May 5;369(6475):64-7.

Slide credit: Adapted from Walters, M, OPM CUW, 2022.

Testing Method – What test?

Microarrays

Cheaper than sequencing
Used in GWAS research, genetic expression profiling

Sequencing

Ex. Sanger sequencing, NGS
Queries a broad group of genes simultaneously
VUS and secondary findings
Leveraged for genotyping panels

Cytogenetic testing and FISH

Provides ability to obtain a global view of chromosomal number and structure
Specialized labor and expertise required to perform the analysis

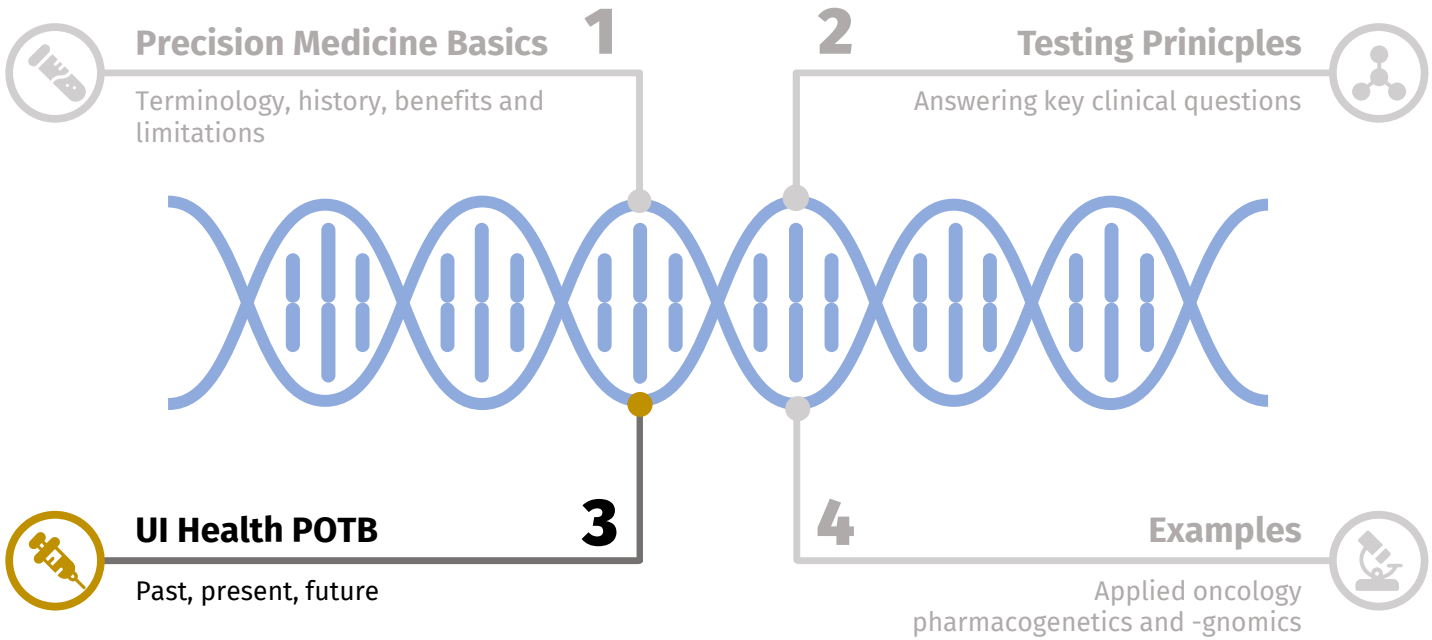
Slide credit: Adapted from Walters, M, OPM CUW, 2022.

What Specimen and when?

	Germline	Somatic
Rationale	1) Disease predisposition for family members 2) Drug selection (BRCA associated)	1) Drug selection
Timing	Part of diagnostic work-up, but can be performed anytime	Recent biopsy is important
Tissue Source	Blood (WBCs) or buccal	Tissue (formalin fixed or fresh frozen) or liquid biopsy (blood for cf DNA)
Frequency	Once	Diagnosis, progression

Slide credit: Adapted from Walters, M, OPM CUW, 2022.

Outline



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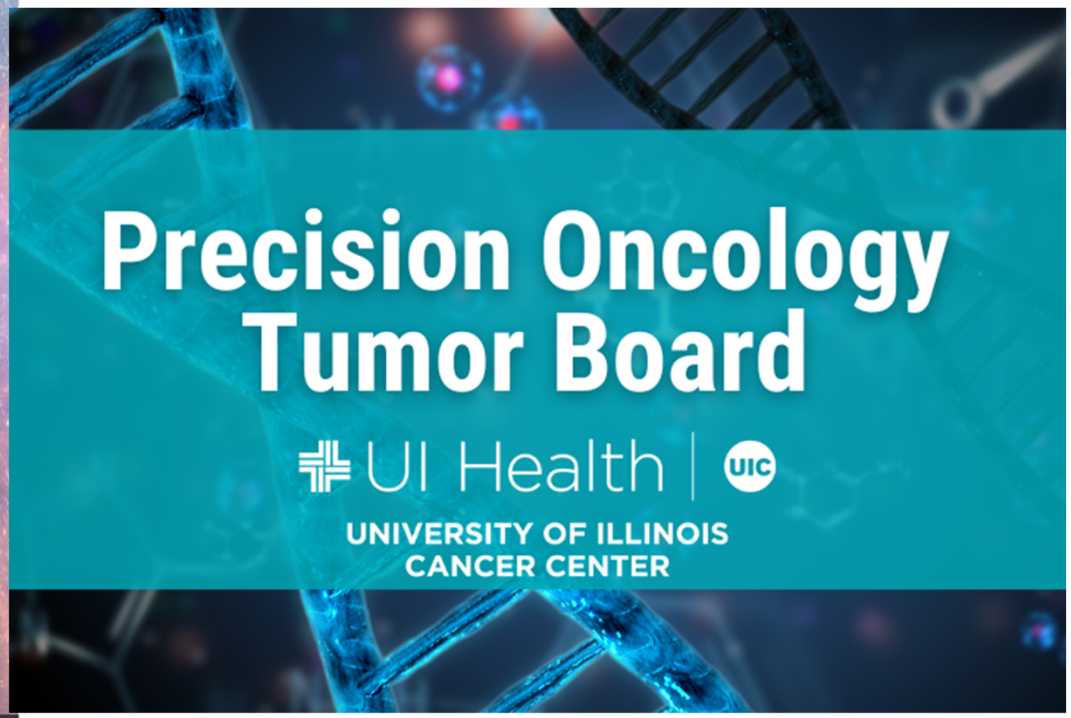
UIC's Precision Oncology Tumor Board (POTB)



Why is there a need for POTB?

Cancer care can change in a weekend…

In May 2021, **the FDA**

mutated, locally adva

systemic therapy.[3]

FDA ODAC Panel Votes Against Sotorasib Data in KRAS G12C+ Advanced NSCLC

October 7, 2023
Kristi Rosa

News *Article*

The FDA Oncologic Drugs Advisory Committee voted 10-to-2 that findings from the phase 3 CodeBreaK 200 trial cannot be reliably interpreted.

FDA ODAC Panel Votes Against Sotorasib Data in KRAS G12C+ Advanced NSCLC

According to the FDA's Oncologic Drugs Advisory Committee (ODAC), the progression-free survival (PFS) data from the phase 3 CodeBreaK 200 trial (NCT04303780) evaluating sotorasib (Lumakras) vs docetaxel for the treatment of patients with pretreated, locally advanced or metastatic *KRAS* G12C–mutated non–small cell lung cancer (NSCLC) cannot be reliably interpreted.

The panel recently held a vote, in which participants voted 10-to-2 against the reliability of the results.

with *KRAS* G12C–

d at least 1 prior

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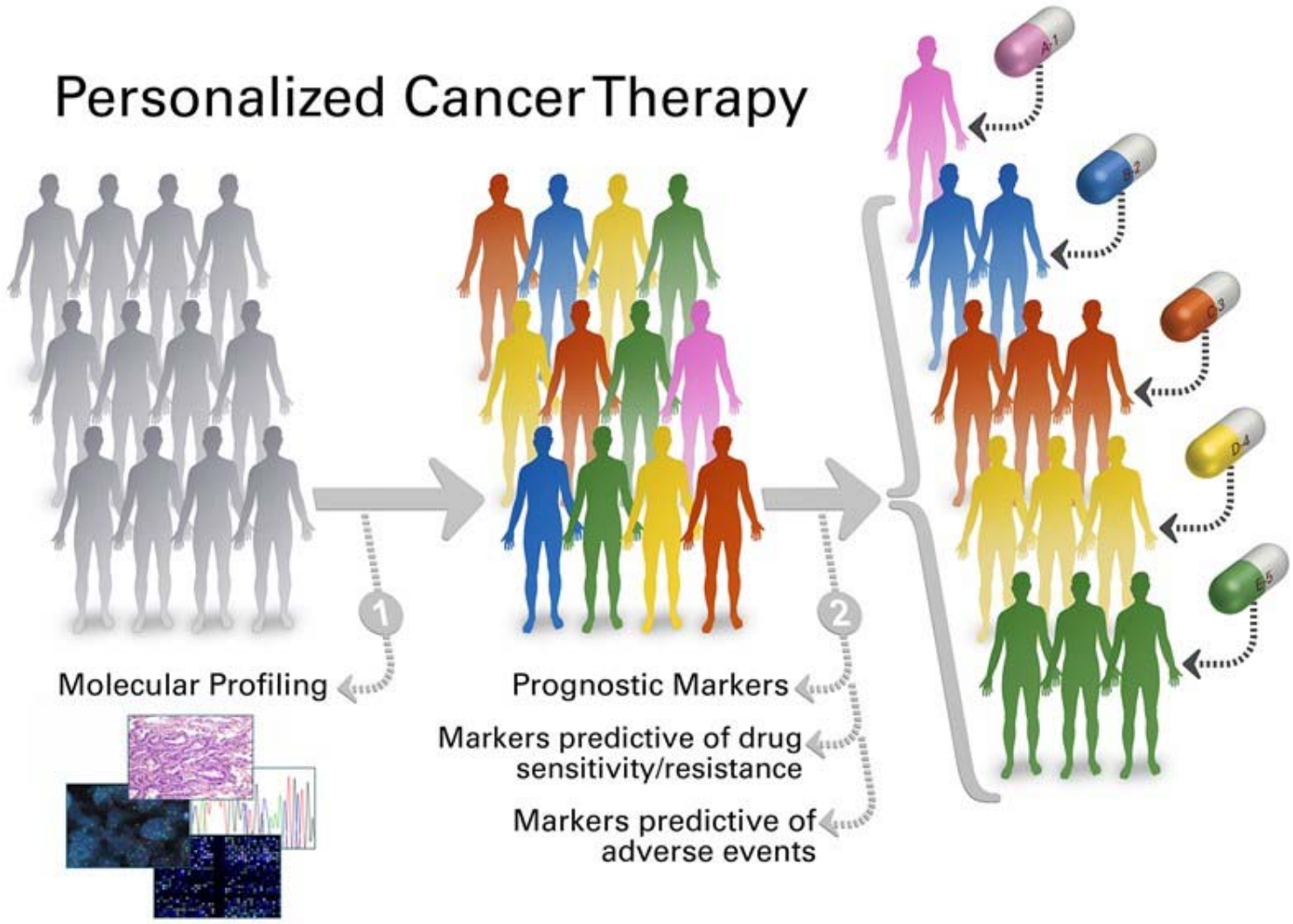
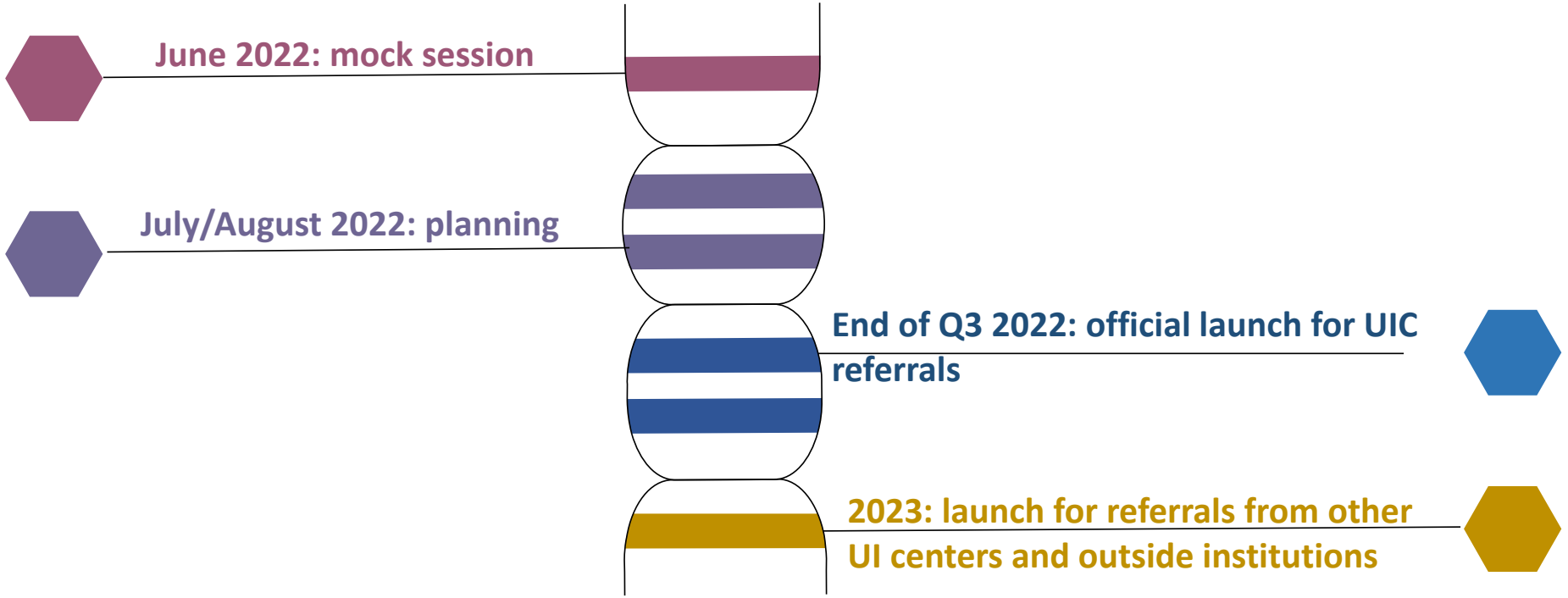


Source: MD Anderson

UIC POTB Launch Timeline



Tentative plan for monthly session

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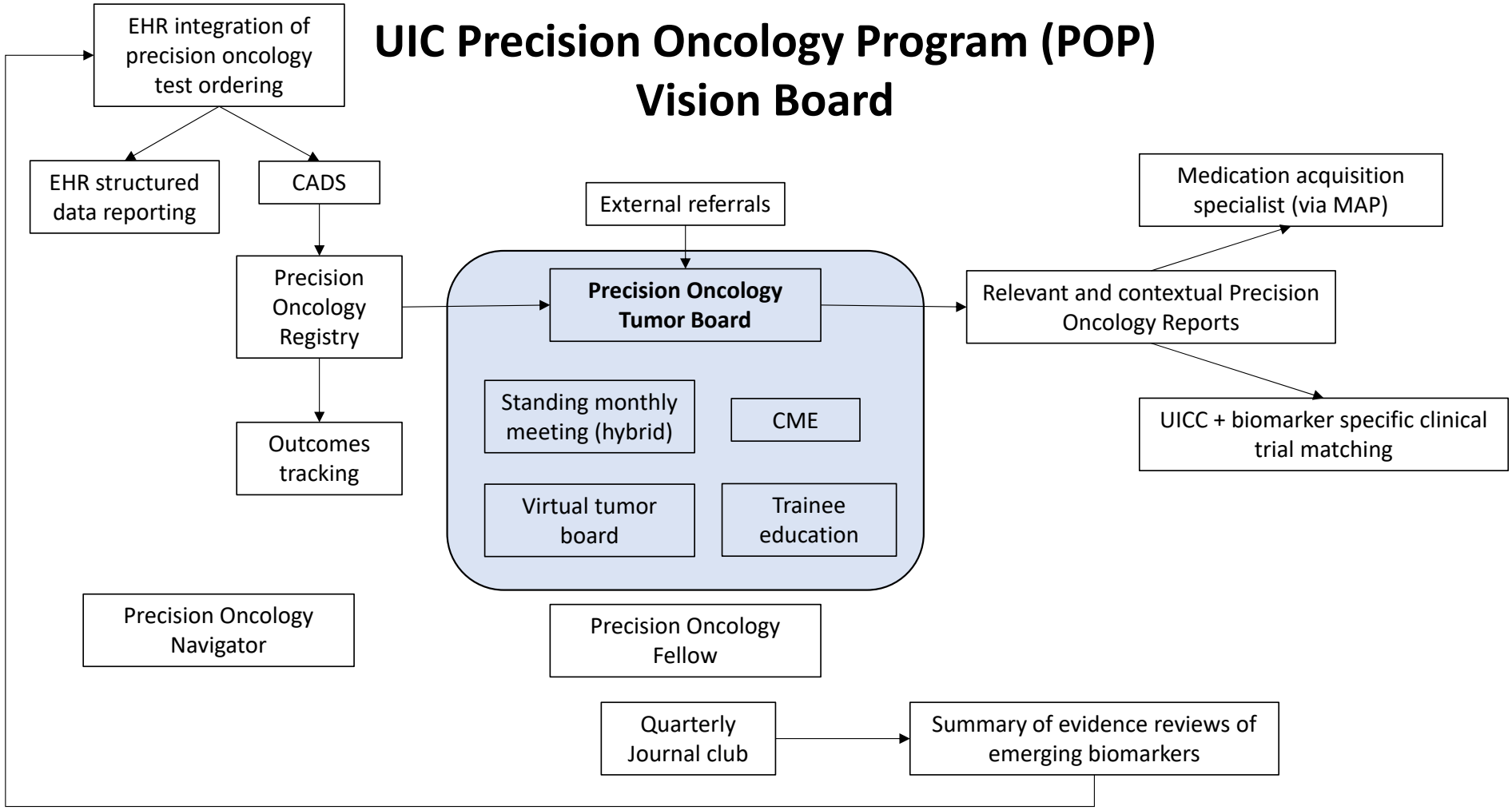
UIC Precision Oncology Program (POP) Vision Board



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Tumor Board Discussion Summary

UIC Precision Oncology Tumor Board Discussion Summary

Re: PATIENT NAME, DOB ***, MRN ***

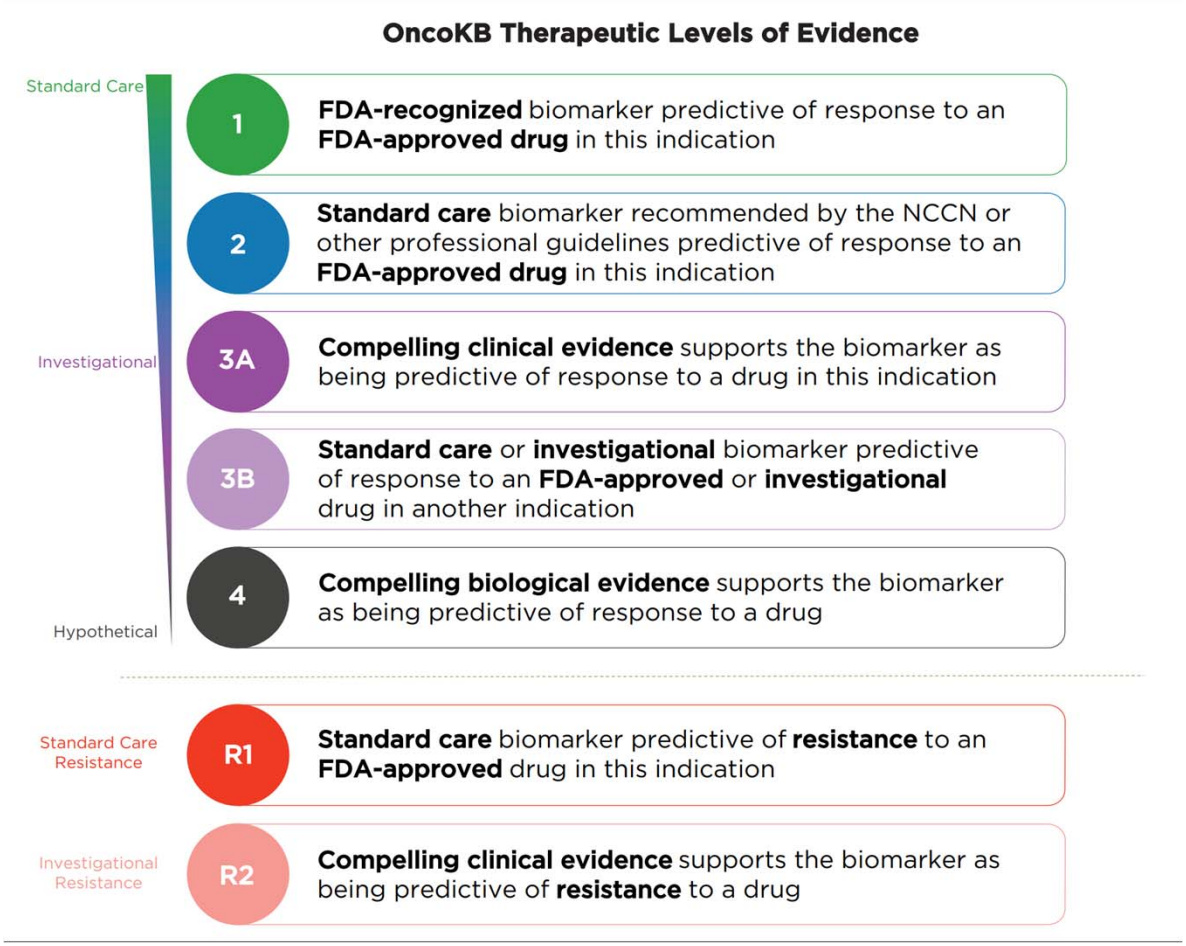
Dear Dr. NAME

Thank you for your referral to the UIC Precision Oncology Tumor Board (POTB). The case was discussed by the POTB specialists on DATE.

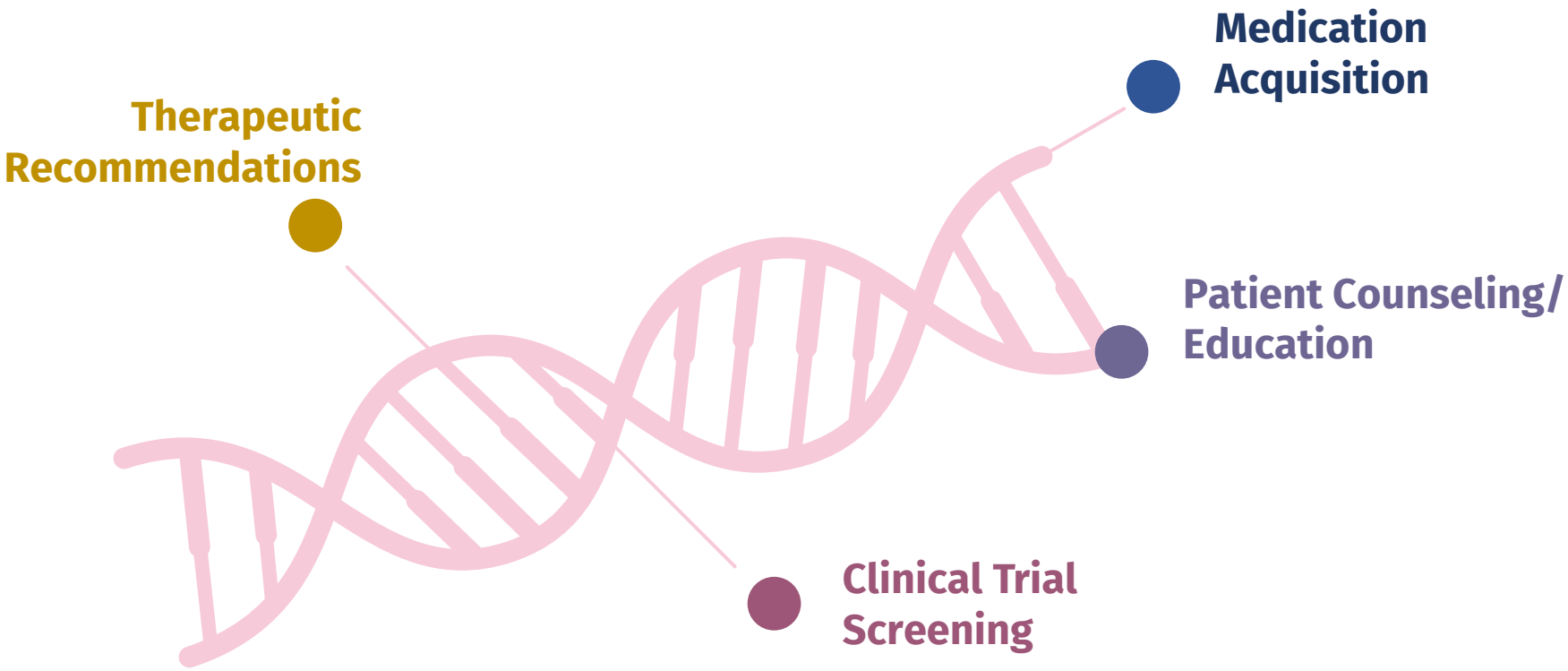
Your patient has the following type of actionable biomarkers:

FDA-recognized biomarker associated with sensitivity to an FDA-approved drug
Biomarker with compelling clinical evidence suggesting sensitivity to therapy (off-label use)
Biomarkers that match clinical trial enrollment criteria
Biomarker associated with off-target treatment implications
Biomarker with potential germline implications
Other
None

OncoKB Therapeutic Levels of Evidence



Pharmacist Integration



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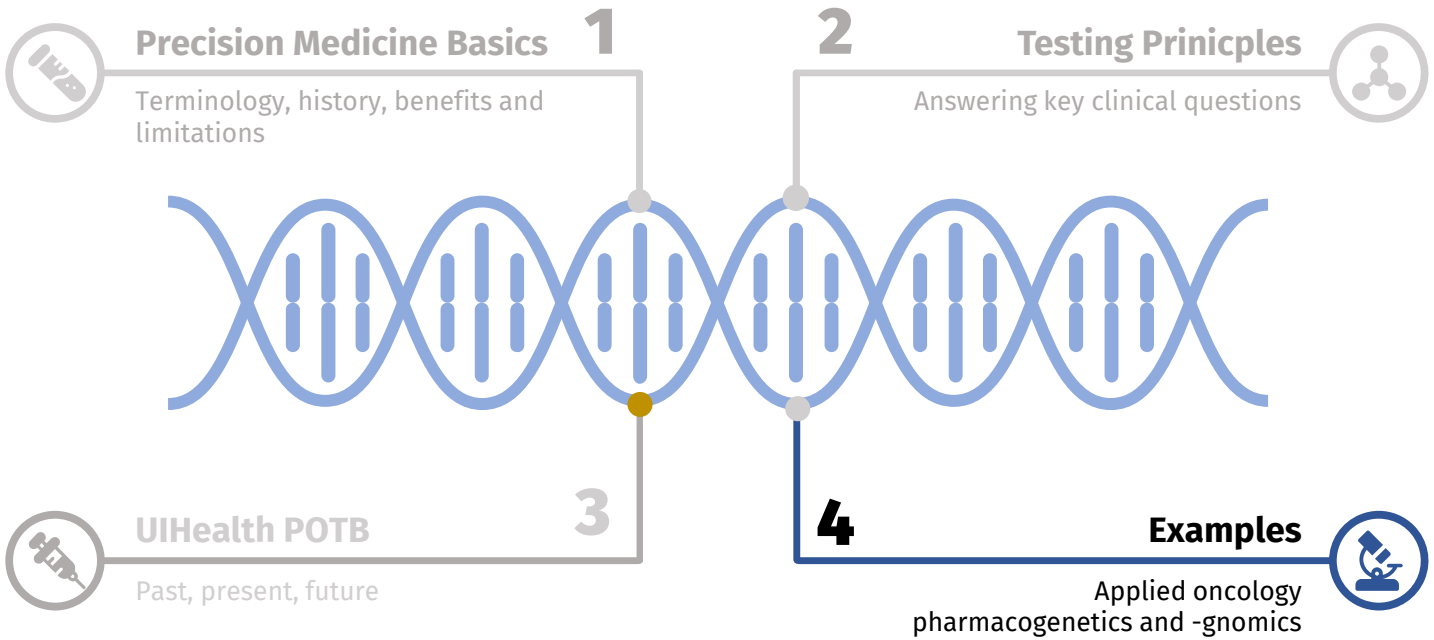
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Example Case 1

UIC POTB

- Three cases
  - Case presentation by referring oncologist (if available)
  - Molecular background
  - Therapeutic implications review by clinical pharmacist
  - Discussion
- Cases + discussion will be kept to ~10 minutes to allow for adequate time

Case 1: YL (Dr Feldman)

Diagnosis: NSCLC, lung adenocarcinoma

Clinical stage: Initial dx cT2a N0 (stage IB) → recurrence contralateral lung stage IVA

Clinical history:
-s/p lobectomy for original dx, lung adenoca w/ EGFR L858R
-recurrence ~1.5y later w/ 2 new lung nodules, enrolled in clinical trial and randomized to Osimertinib arm
-CT ~1.5y after w/ increasing RLL lesions, bx proven lung adenoca → plan for RFA

Biomarker result of interest: EGFR L718V exon 18

Clinical question: role of EGFR L718V mutation in Osimertinib resistance?

Case 1: YL (Dr Feldman)

Tier I: EGFR p.L858R
Tier II: MSH2 p.E809K, MSH6 p.E1163V
Tier III: A p.H384fs, AR p.S176R, BRCA2 c.8954-delAACA, NOTCH3 p.R75Q, PMS2 p.H139D, PTCH1 p.T416S, PTEN p.V21F, RB1 p.F473fs, TP53 p.Y126*

GENOMIC VARIANTS

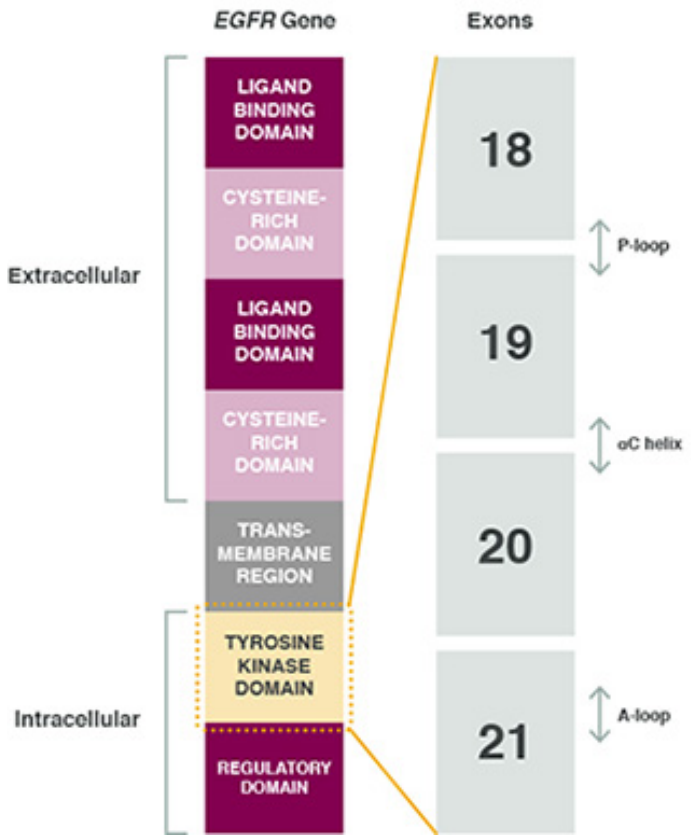
Somatic - Potentially Actionable			Variant Allele Fraction
EGFR	p.L858R	Missense variant (exon 21) - GOF	22.7%
EGFR	p.L718V	Missense variant (exon 18) - GOF	12.8%

Case 1: YL (Dr Feldman)
Tempus xT

Sample:	
RLL mass	
Immunotherapy Biomarkers:	
1. PDL1 TPS <1%, MMR normal, TMB 2.1m/MB	
Tier I Variants:	
1. EGFR L858R, exon 21 2. EGFR L718V, exon 18	
Tier II Variants:	**Tier III Variants:**
1. n/a	1. n/a

Germline testing done or indicated?

Gene Background



Distribution of mutation types*

Mutation type	Frequency
Exon 18: G719X	~2%
Exon 19 deletions	45–46%
Exon 20: S768I T790M Insertions	<1% 4% ~1%
Exon 21: L858R L861Q	38–45% 1%

EGFR-Mutations.com

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ELSEVIER

Lung Cancer

Volume 118, April 2018, Pages 1-5

Acquired *EGFR* L718V mutation mediates resistance to osimertinib in non-small cell lung cancer but retains sensitivity to afatinib

Yutao Liu [a, 1], Yan Li [b, 1], Qiuxiang Ou [c], Xue Wu [c], Xiaonan Wang [d], Yang W. Shao [c, e], Jianming Ying [b]

EGFR L718V (+)/T790M (–) as a Mechanism of Resistance in Patients with Metastatic Non–small-cell Lung Cancer with EGFR L858R Mutations

Luis E. Raez • Carlos Carracedo • Leylah M. Drusbosky • Michel Velez • Jennifer Carlisle • Thomas Stinchcombe

Published: April 08, 2021 • DOI: https://doi.org/10.1016/j.cllc.2021.03.018 • Check for updates

Therapeutic Implications

FDA-Approved Therapies, Current Diagnosis			
Class	**Drug**	**Mutation**	**Level of Evidence**
EGFR Inhibitor	Afatinib	EGFR p.L718V Gain-of-function EGFR p.L858R L858R - GOF	NCCN, Consensus, Non-Small Cell Lung Cancer MSK OncoKB, Level 1
	Dacomitinib		
	Erlotinib		
	Gefitinib		
	Osimertinib		
Combination (EGFR Inhibitor + VEGFR2 Inhibitor)	Erlotinib + Ramucirumab		

Therapeutic Implications:

Durable clinical benefit from afatinib in a lung adenocarcinoma patient with acquired *EGFR* L718V mutation-mediated resistance towards osimertinib: a case report and literature review

- 5 case reports in the literature:
  - Raez et al. demonstrated that 2 of 3 NSCLC patients with EGFR L718V respond to afatinib with disease stabilization
  - Fang et al. revealed that the use of afatinib in an EGFR-mutated LUAD patient with acquired L718V mutation yielded a PFS of at least 6 months
  - Song et al. showed durable response to afatinib with a PFS of 18 months and counting

Ann Palliat Med. 2022;11(3):1126-1134. doi:10.21037/apm-21-3731

Clinical Trial Implications

Trials For Tier I Variant				
Clinical Trial	**Disease State**	**Pt Mutation**	**Phase**	**Study Contact**
Phase 2 Platform Study in Patients With Advanced Non-Small Lung Cancer Who Progressed on First-Line Osimertinib Therapy (ORCHARD) (NCT03944772)	NSCLC	EGFR p.L858R mutation EGFR p.L718V mutation	Phase II	Contact: AstraZeneca Clinical Study Information Center 1-877-240-9479 information.center@astrazeneca.com **Recruiting** Research Site Chicago, Illinois, United States, 60612

POTB Clinical Question and Therapeutic Implications

- **Clinical question:** role of EGFR L718V mutation in Osimertinib resistance?
- **Therapeutic Implications Summary:**
  - Therapy after progression on osi stratified based on sx, CNS involvement, and extent of mets
    - NCCN recommend **definitive local therapy and cont of osimertinib** as an option
  - Acquired *EGFR* L718V mutation-mediated resistance towards osimertinib derived durable response to the 2nd gen EGFR-TKI afatinib in several case reports

Case Discussion

Example Case 2

Case 2: B.S. (Dr Weinberg) 73M w/ L neck LAD

Diagnosis: lung adenocarcinoma vs medullary thyroid carcinoma

Clinical stage: IVb (pT2N1b)

Clinical history:
-Presented to ENT w/ L neck lump, bx showed lung adenocarcinoma
-PET w/ L neck, SC, mediastinal LAD + LUL nodule
-s/p thyroidectomy

Biomarker result of interest: xT: RET C630R, xG+ MITF heterozygous

Clinical question: Consideration for TKI. Discussion about how initial diagnosis was NSCLC/poorly differentiated carcinoma and need to use clinical assessment and not always histologic diagnosis to guide work-up.

Case 2: B.S. (Dr Weinberg) 73M w/ L neck LAD

- Pathology sample – Left Neck Lymph Node

A. Left Neck Lymph Node, Biopsy:

- Entire sample consists of metastatic poorly differentiated carcinoma consistent metastatic lung adenocarcinoma
  - Tumor desmoplasia is identified
  - Negative for residual lymphoid tissue

Molecular Findings
Tempus xT

Sample:	
L neck LN	
Immunotherapy Biomarkers:	
1. PDL1 <1% 2. TMB 3.7 m/MB 48% 3. MSI Stable	
Tier I Variants:	
1. RET p.C630R	
Tier II Variants:	**Tier III Variants:**
1. N/A	1. N/A

Germline Findings

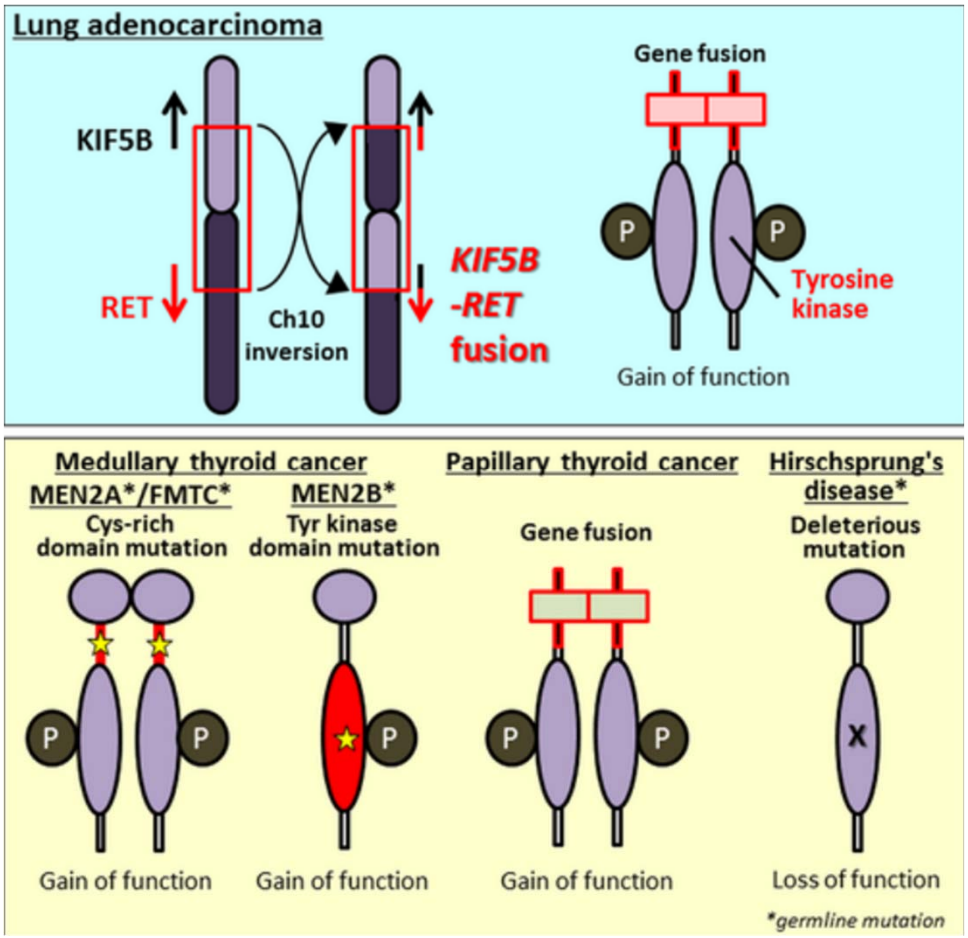
Tempus xG

Gene	Variant	Zygosity	Classification
MITF	c.3 G>A p.M1?	Heterozygous	Likely Pathogenic Variant

Interpretation

This individual is heterozygous for a likely pathogenic variant in MITF. Although this gene is associated with multiple autosomal dominant phenotypes/disorders, the type of variant identified in this individual is predicted to be associated with loss-of-function (LOF) and Waardenburg spectrum disorder. While LOF variants in MITF have not been shown to be associated with autosomal dominant MITF-related cancer susceptibility, we cannot exclude the possibility that this variant might be associated with increased risk for MITF-related cancers.

RET Fusion vs Point Mutation



Kohono Cancer Science 2013

Case Report

Case Rep Oncol. 2018 May-Aug; 11(2): 399–403.
Published online 2018 Jun 22. doi: 10.1159/000490238
PMCID: PMC6047557
PMID: 30022943

Genomic Profiling Reveals Medullary Thyroid Cancer Misdiagnosed as Lung Cancer

Eva J. Gordon,[a,*] David Parker,[a] Kelly Barth,[a] Jennifer Pena,[a] Julia A. Elvin,[b] Thomas DeLeon,[c] and Nina J. Karlin[c]

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- 70YM p/w L shoulder/neck pain --> CT w/many small lung nodules, mediastinal LAD, 3.3cm thyroid nodule
- Pathology (Thyroid, Lung) described as poorly differentiated adeno likely lung primary
- NGS --> RET point mutation C630R
- Treated as MTC w/vandetanib w/ 6-month response

Therapeutic Implications

FDA Approved Therapies, Current Indication		
RET Inhibitor	Pralsetinib	NCCN Consensus, Thyroid Medullary Cancer RET p.C630R Gain of function
	Selpercatinib	NCCN Consensus, Thyroid Medullary Cancer RET p.C630R Gain of function

Therapeutic Implications: ARROW

Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study

Table 11: Efficacy Results for RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib (ARROW)

Efficacy Parameters	GAVRETO (N=55)
Overall Response Rate (ORR)* (95% CI)	60 (46, 73)
Complete Response, %	1.8
Partial Response, %	58
Duration of Response (DOR)	(N=33)
Median in months (95% CI)	NR (15.1, NE)
Patients with DOR ≥ 6 months‡, %	79

NR = Not Reached; NE = Not Estimable

* Confirmed overall response rate assessed by BICR

‡ Based on observed duration of response

Table 12: Efficacy Results for Cabozantinib and Vandetanib-naïve RET-Mutant MTC (ARROW)

Efficacy Parameters	GAVRETO (N=29)
Overall Response Rate (ORR)* (95% CI)	66 (46, 82)
Complete Response, %	10
Partial Response, %	55
Duration of Response (DOR)	(N=19)
Median in months (95% CI)	NR (NE, NE)
Patients with DOR ≥ 6 months‡, %	84

NR = Not Reached; NE = Not Estimable

* Confirmed overall response rate assessed by BICR

† Based on observed duration of response

The lancet Diabetes & endocrinology 9.8 (2021): 491-501.

Therapeutic Implications: LIBRETTO 001 MTC

A Study of Selpercatinib (LOXO-292) in Participants With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer

Table 11: Efficacy Results in LIBRETTO-001 (RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)

	RETEVMO (n = 55)
Overall Response Rate[1] (95% CI)	69% (55%, 81%)
Complete response	9%
Partial response	60%
Duration of Response	
Median in months (95% CI)	NE (19.1, NE)
% with ≥6 months[2]	76

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Table 12: Efficacy Results in LIBRETTO-001 (Cabozantinib and Vandetanib-naïve RET-Mutant MTC)

	RETEVMO (n = 88)
Overall Response Rate[1] (95% CI)	73% (62%, 82%)
Complete response	11%
Partial response	61%
Duration of Response	
Median in months (95% CI)	22.0 (NE, NE)
% with ≥6 months[2]	61

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

N Engl J Med 2020; 383:825-835

LIBRETTO 001: Other Solid Tumor

Tumour-agnostic efficacy and safety of selpercatinib in patients with *RET* fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial

Table 14: Efficacy Results in LIBRETTO-001 (Other RET Fusion-Positive Solid Tumors)

	RETEVMO (n = 41)
Overall Response Rate[1] (95% CI)	44% (28, 60)
Complete response	4.9%
Partial response	39%
Duration of Response	
Median in months (95% CI)	24.5 (9.2, NE)
% with ≥6 months[2]	67%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

The Lancet Oncology, *23*(10), 1261-1273.

Table 15: Efficacy Results by Tumor Type in LIBRETTO-001 (Other RET Fusion-Positive Solid Tumors)

Tumor Type	Patients (n = 41)	ORR[1,2]		DOR Range (months)
		n (%)	95% CI	
Pancreatic adenocarcinoma	11	6 (55%)	(23, 83)	2.5, 38.3+
Colorectal	10	2 (20%)	(2.5, 56)	5.6, 13.3
Salivary	4	2 (50%)	(7, 93)	5.7, 28.8+
Unknown primary	3	1 (33%)	(0.8, 91)	9.2
Breast	2	PR, CR	NA	2.3+, 17.3
Sarcoma (soft tissue)	2	PR, SD	NA	14.9+
Xanthogranuloma	2	NE, NE	NA	NA
Carcinoid (bronchial)	1	PR	NA	24.1+
Carcinoma of the skin	1	NE	NA	NA
Cholangiocarcinoma	1	PR	NA	5.6+
Ovarian	1	PR	NA	14.5+
Pulmonary carcinosarcoma	1	NE	NA	NA
Rectal neuroendocrine	1	NE	NA	NA
Small intestine	1	CR	NA	24.5

+ denotes ongoing response.

[1] Confirmed overall response rate assessed by BIRC.

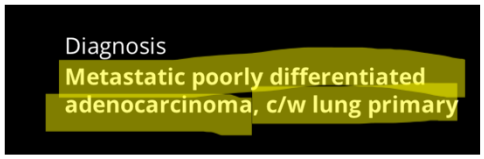
[2] Best overall response for each patient is presented for tumor types with ≤2 patients.

Clinical Trial Implications

CLINICAL TRIALS	
A Study of Selpercatinib (LOXO-292) in Participants With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001) (NCT03157128)	**Phase I/II** Chicago, IL - 7 mi ✓ **RET mutation**
Study of TPX-0046, A RET/SRC Inhibitor in Adult Subjects With Advanced Solid Tumors Harboring RET Fusions or Mutations (NCT04161391)	**Phase I/II** Chicago, IL - 7 mi ✓ **RET mutation**
TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer (NCT02693535)	**Phase II** Chicago, IL - 40 mi ✓ **RET mutation**

POTB Clinical Question and Therapeutic Implications

- **Clinical question:** Consideration for TKI. Discussion about how initial diagnosis was NSCLC/poorly differentiated carcinoma and need to use clinical assessment and not always histologic diagnosis to guide work-up.
- **Therapeutic implications summary:**
- RET inhibitors are approved in the setting of
  - **RET fusion**: aNSCLC (1L), thyroid cancer (1L), advanced solid malignancy w/o other tx options
  - **RET mutant:** medullary thyroid
- Caution when interpreting NGS reports. Must look at the whole picture.



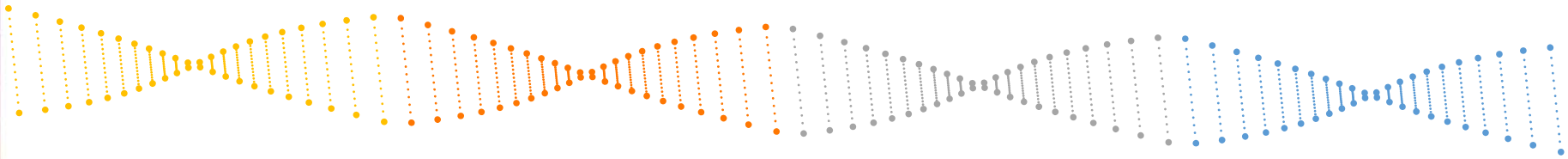
FDA-APPROVED THERAPIES, OTHER INDICATIONS

RET Inhibitor	**Pralsetinib**	NCCN, Consensus, Thyroid Medullary Cancer RET p.C630R Gain-of-function
	Selpercatinib	NCCN, Consensus, Thyroid Medullary Cancer RET p.C630R Gain-of-function

Case Discussion

ICHP Spring Meeting 2024

Resources and Future Directions



Germline Precision Medicine Resources

ClinVar
Clinically relevant variation
CTGATGG
AGGTACG
AGGGCTG
CATGGTG
CAGGTTG
GCACTGA

CPIC®

PG KB

Somatic Oncology Precision Medicine Resources

OncoKB
Precision Oncology Knowledge Base

cBioPortal
for Cancer Genomics

COSMIC
Catalogue Of Somatic Mutations In Cancer

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Personalized Cancer Therapy
Knowledge Base for Precision Oncology

ICHP Spring Meeting 2024

Other Precision Medicine Resources

Future Directions

- Enhanced Molecular Profiling
- Continued Development of New Targeted Therapies
- Expanded Clinical Trial Designs
- Refined Liquid Biopsy Techniques
- Integration of AI and Language Learning Models
- Enhanced Data Sharing
- Integration of Multi-Omic Data
- Focus on Value Based Medicine

Precision Oncology: Who, How, What, When, and When Not?. *Am Soc Clin Oncol Educ Book* **37**, 160-169(2017).

Questions?

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