



Precision Medicine:

The Future of Healthcare is Here

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System Medical Director of Precision Medicine
Endowed Professor of Experimental Therapeutics
Ochsner Health

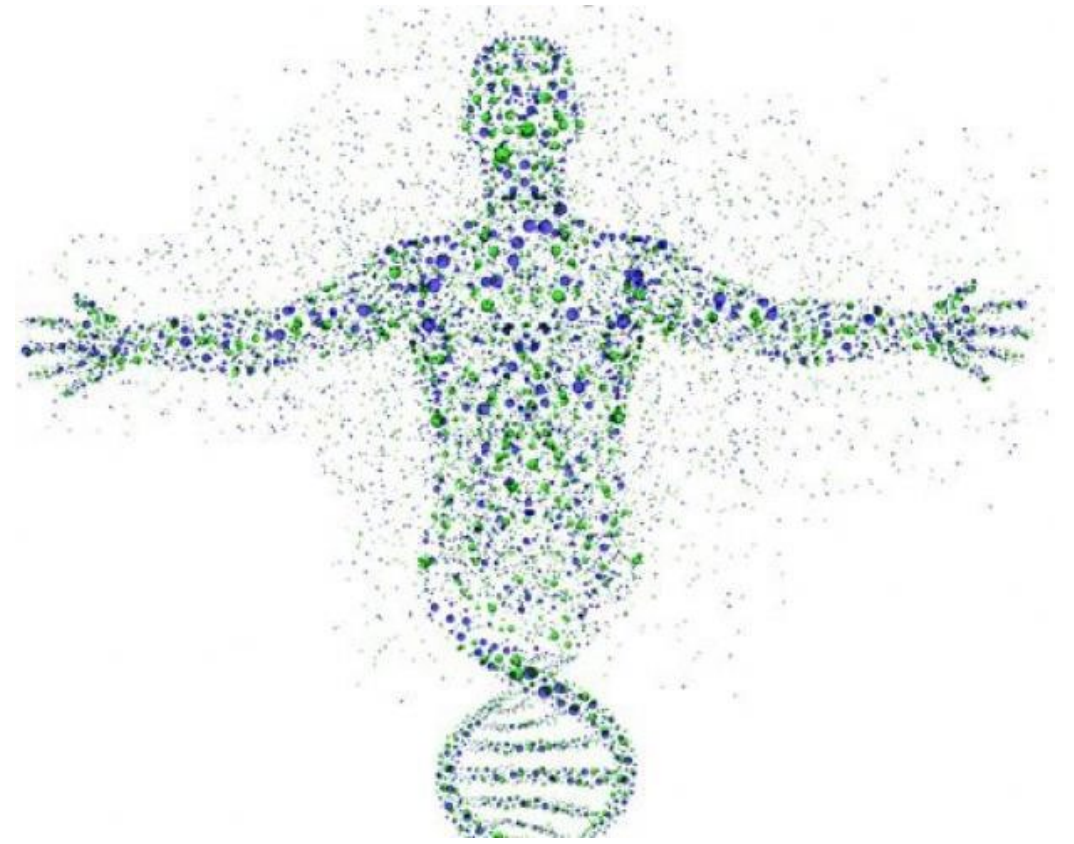
Disclosures

Consulting and Speakers Bureaus	AstraZeneca, Merck, BMS, Astellas, Eisai, Janssen, SeaGen, Exelixis, EMD Serono, Daiichi Sankyo, Pfizer, Novartis



Agenda

- Overview
- NGS and Cancer: Just the Beginning
- MRD Testing
- MCED Screening Tests
- Pharmacogenomics
- WGS in NICU
- Hereditary
- The Future



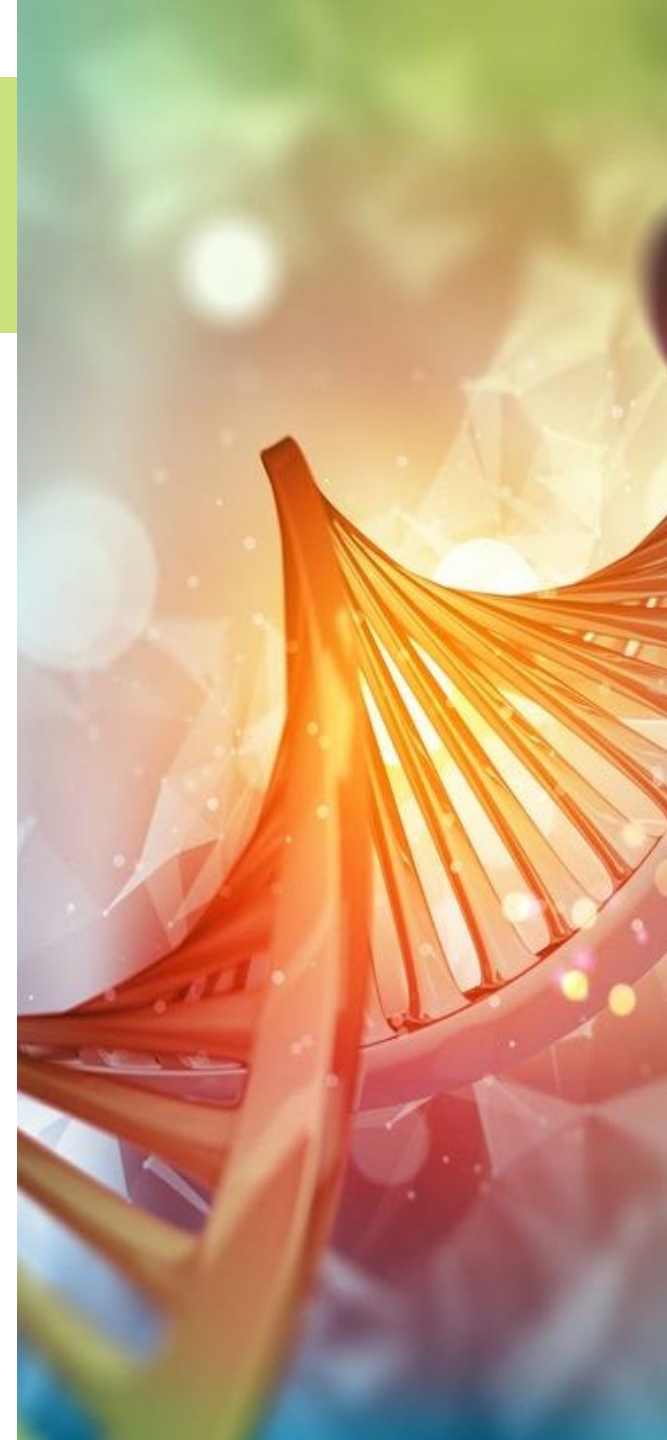
Precision Medicine Overview



What is Precision Medicine?

- Uncovers the underlying molecular alterations that drive health and disease
- Tailors health care on an individual patient level
- Most rapidly involving field in medicine, having a bigger impact each and every week.

No field in medicine will be untouched by this revolution.



Precision Medicine Market Overview



\$141.70B
TAM by 2026



42%
of the drugs in the
development pipeline
include biomarkers
in their design.



10
new precision medicine
diagnostic tests daily



What is Precision Medicine?

Risk Assessment

- Hereditary screening for risk stratification
- Population based screening

Diagnosis

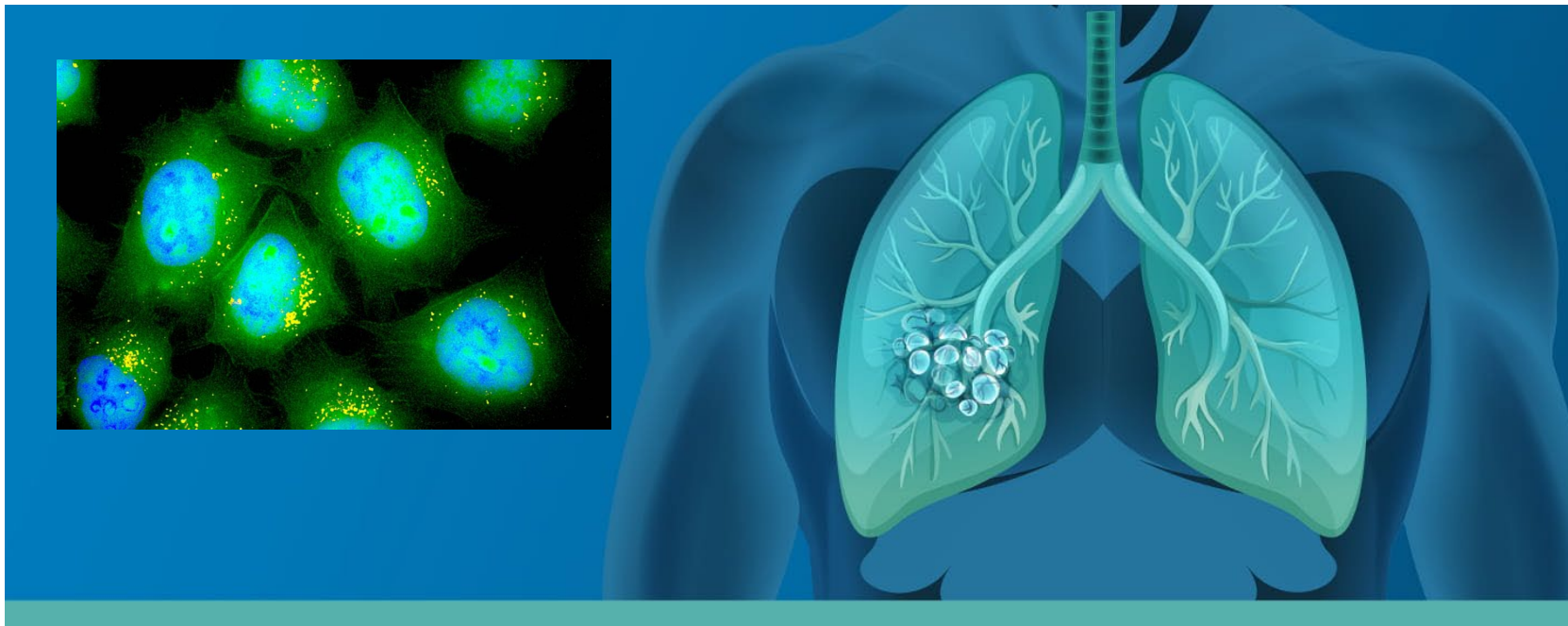
- Multi-cancer early detection (MCED)
- Rapid whole genome sequencing (WGS) in neonates and others
- Early detection of disease

Treatment

- Pharmacogenomics (PGx)
- Next-generation sequencing (NGS)
- Single gene-drug pairs

Getting the best medicine to each individual patient at the right time and the right dose based on advanced molecular and genomic technologies.

NGS and Cancer



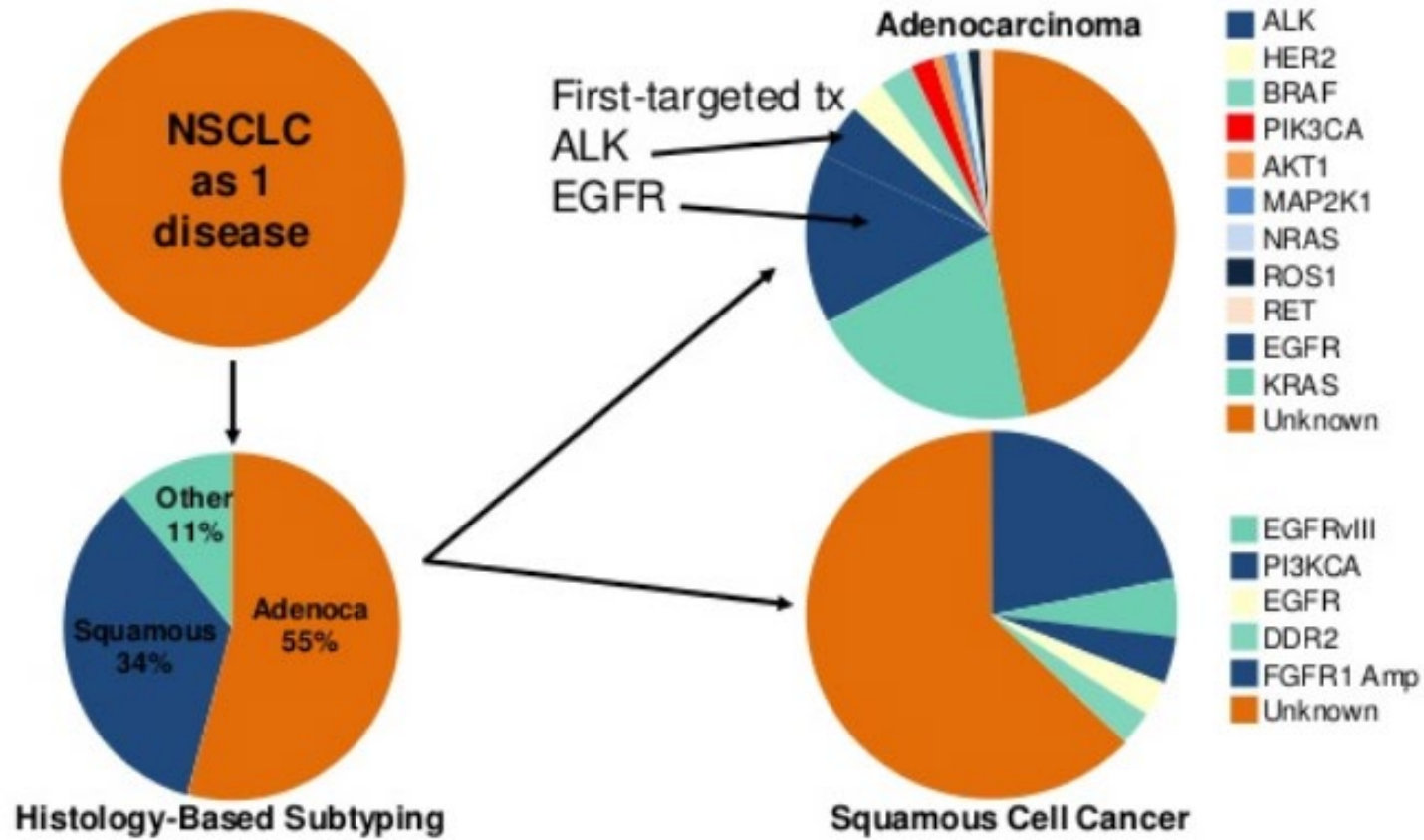
Next Generation Tumor Sequencing

- One very important tool for precision medicine in cancer.
- Allows for testing hundreds of gene mutations from a single tissue sample or even from naked tumor DNA found in serum or urine.
- Provides the most personalized therapy options available.
- Studies have shown that the NGS is reliable and often finds actionable mutations at a higher rate than ordinary methods
- Costs are dropping drastically ~ \$1k
- Allow for stratification to clinical trials

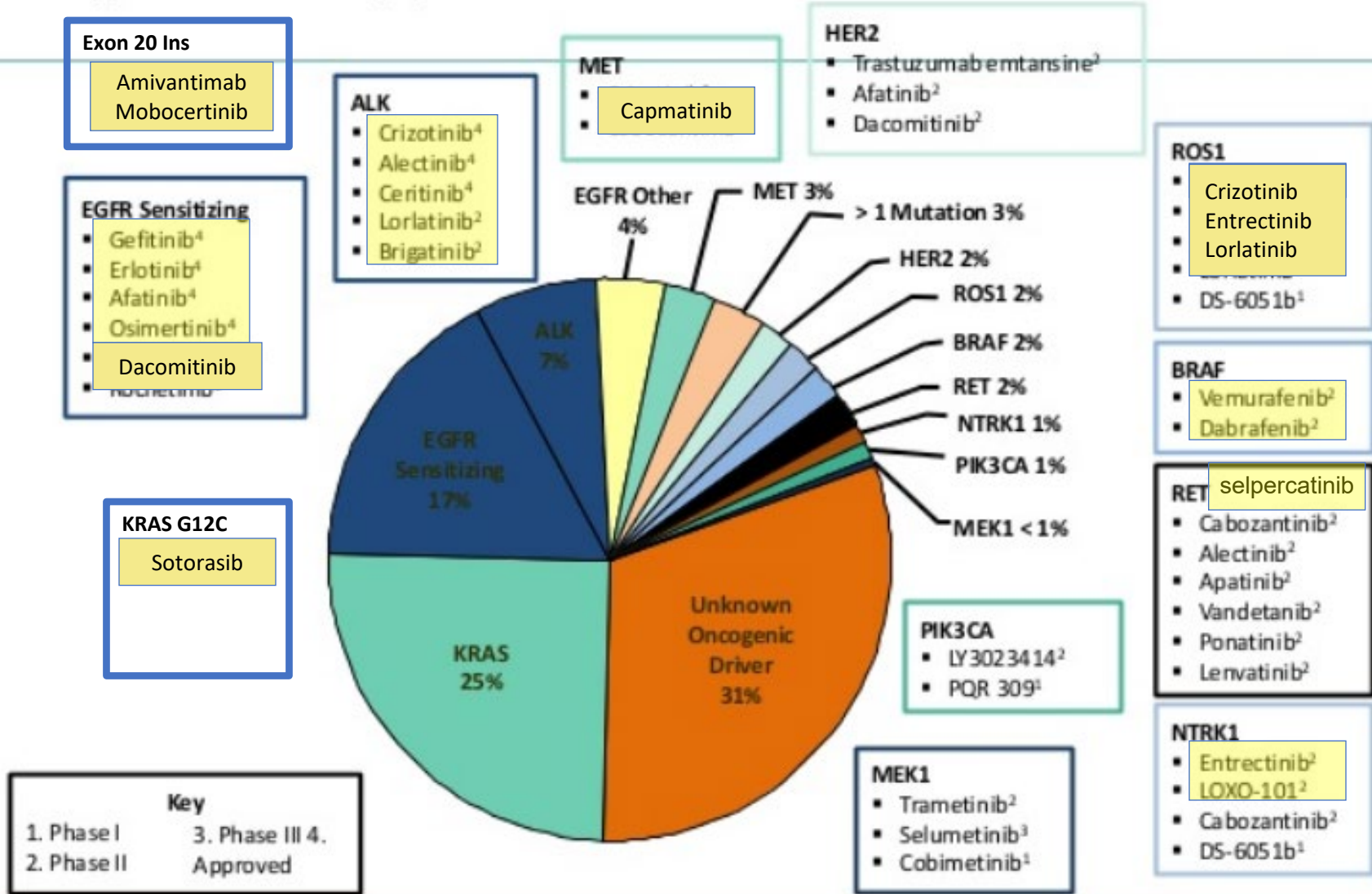
Patient Selection is KEY

- Testing EVERY patient for EVERY actionable mutations is recommended PRIOR to beginning systemic therapy.
- Setting up systems to automate and integrate testing into workflows is essential.

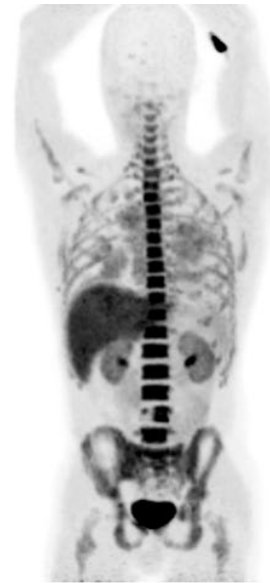
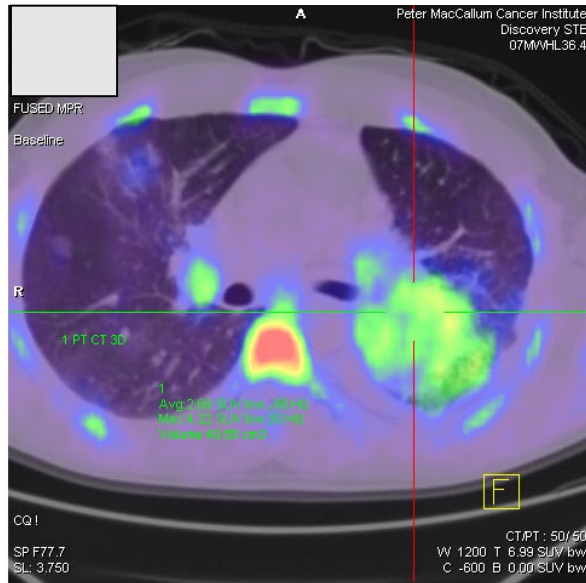
NSCLC Evolution: From Single Disease to Many Molecularly Defined Subsets



Targeted Therapy for Adenocarcinoma

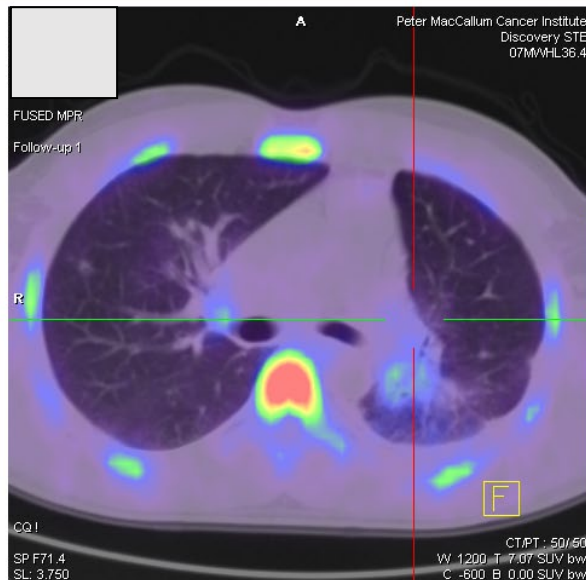


43 yo Male Never Smoker with Stage IV NSCLC Positive for EML4-ALK



Pretreatment

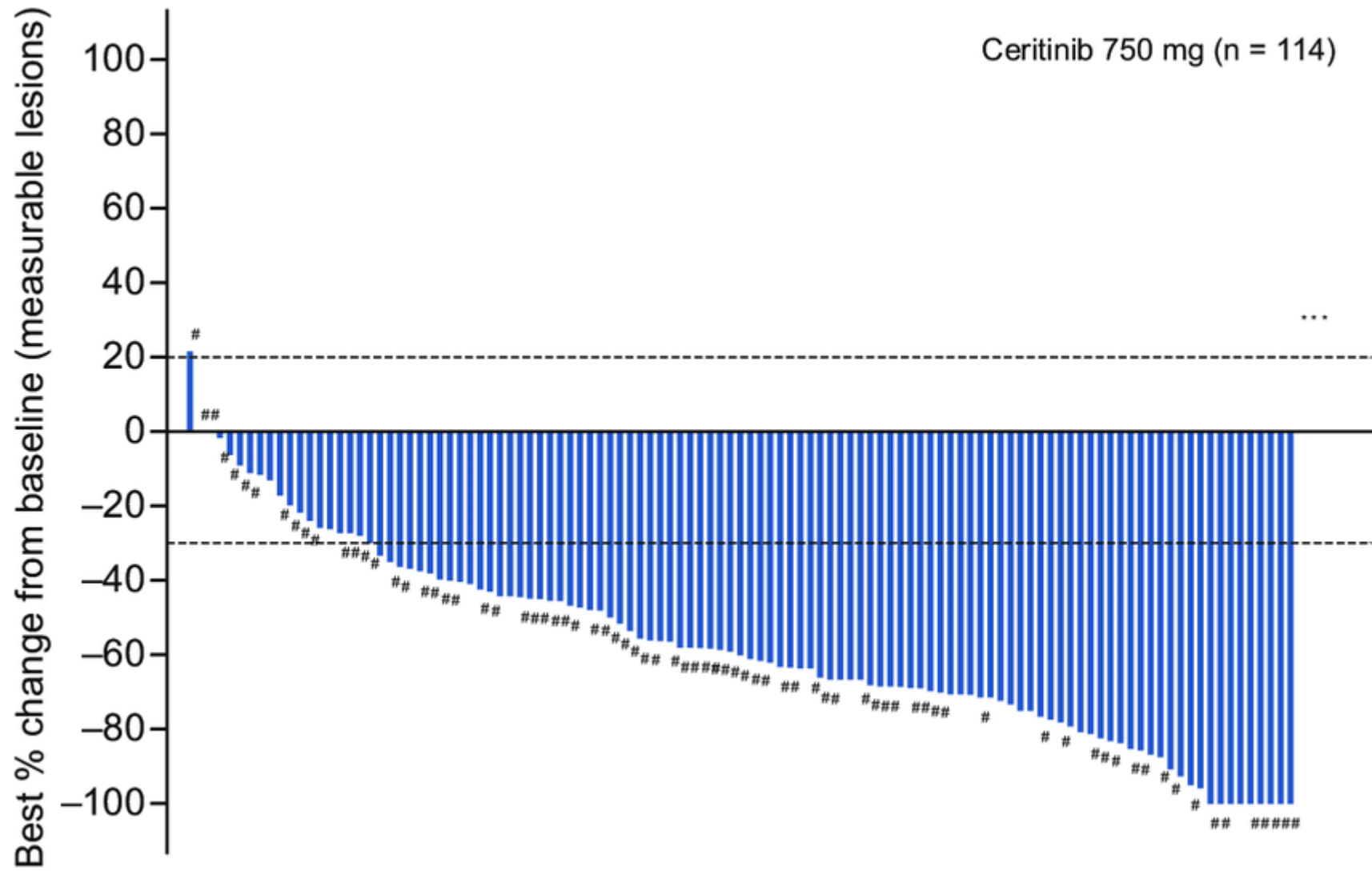
T: 17%
E: 0%



After 1 cycle

T: 28%
E: 0%

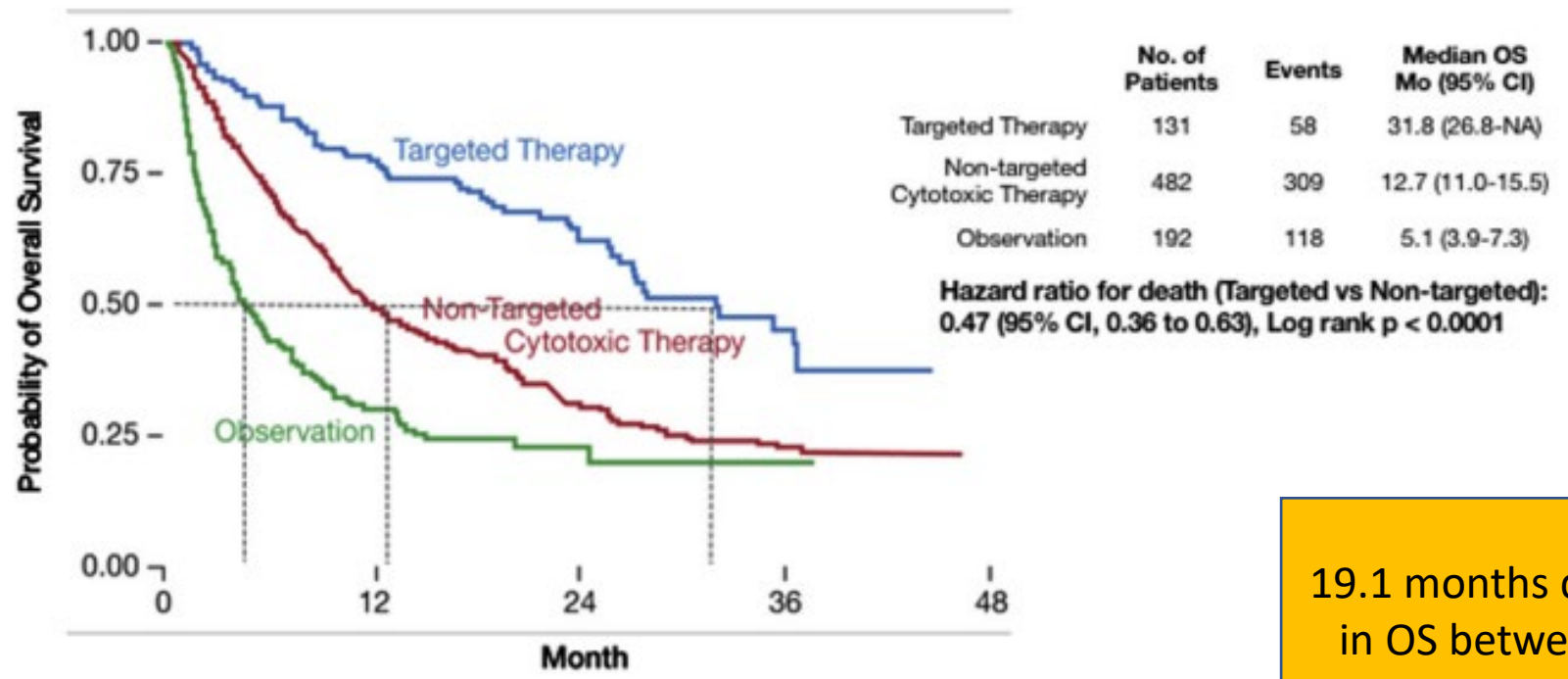
Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall F; PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014 Dec 4;371(23):2167-77. doi: 10.1056/NEJMoa1408440. Erratum in: *N Engl J Med*. 2015 Oct 15;373(16):1582. PMID: 25470694.



Outcomes in NSCLC in Patients with Actionable Driving Mutations

Median OS
31.8 months

Median OS
12.7 months



	No. of Patients	Events	Median OS Mo (95% CI)
Targeted Therapy	131	58	31.8 (26.8-NA)
Non-targeted Cytotoxic Therapy	482	309	12.7 (11.0-15.5)
Observation	192	118	5.1 (3.9-7.3)

No. at Risk	0	12	24	36	48
Targeted Therapy	131	98	56	19	0
Non-targeted Cytotoxic Therapy	482	236	82	37	0
Observation	192	47	9	1	0

19.1 months difference in OS between TT vs non-TT in NSCLC

Gutierrez ME, Choi K, Lanman RB, Licitra EJ, Skrzypczak SM, Pe Benito R, Wu T, Arunajadai S, Kaur S, Harper H, Pecora AL, Schultz EV, Goldberg SL. Genomic Profiling of Advanced Non-Small Cell Lung Cancer in Community Settings: Gaps and Opportunities. Clin Lung Cancer. 2017 Nov;18(6):651-659. doi: 10.1016/j.clc.2017.04.004. Epub 2017 Apr 13. PMID: 28479369.

No-Cost Next Generation Sequencing of Advanced Cancer Patients within the Strata Precision Oncology Network Supports Clinical Trial Enrollment

Marc A. Matrana¹, Scott A. Tomlins², Kat Kwiatkowski², Khalis H. Mitchell², J. Marie Suga³, E. Claire Dees⁴, Mark E. Burkard⁵, Jamil Khatri⁶, Malek M. Safa⁷, Eddy Yang⁸, Benjamin Parsons⁹, Alex R. Menter¹⁰, Michael A. Thompson¹¹, Anneliese O. Gonzalez¹², Timothy Robert Wassenaar¹³, Dan Rhodes²

¹Ochsner Clinic Foundation, New Orleans, LA; ²Strata Oncology, Ann Arbor, MI; ³Kaiser Permanente, Vallejo, CA; ⁴The University of North Carolina at Chapel Hill, Chapel Hill, NC; ⁵University of Wisconsin Carbone Cancer Center, Madison, WI; ⁶Christiana Care Health System, Newark, DE; ⁷Kettering Cancer Center, Kettering, OH; ⁸University of Alabama at Birmingham, Birmingham, AL; ⁹Gundersen Health System, La Crosse, WI; ¹⁰Kaiser Permanente, Denver, CO; ¹¹Advocate Aurora Health, Milwaukee, WI; ¹²The University of Texas, Houston, TX; ¹³ProHealth Care Regional Cancer Center, Waukesha, WI

Background

Recent approvals for tumor agnostic precision therapies have expanded therapeutic options for patients, however, widespread integration of systematized next generation sequencing (NGS) to support continued drug development is hindered by numerous barriers.

The Strata Trial provides no-cost NGS to advanced cancer patients across the Strata Precision Oncology Network™ of 21 academic institutions and clinical cancer centers (Figure 1). This observational study is designed to evaluate the proportion of patients available for targeted therapy clinical trials and to assess the feasibility of using a large-scale NGS screening program to match patients for eligibility assessments (Clinical trial information: NCT03061305).

Aims

- Provide comprehensive tumor sequencing and trial matching for 100,000 advanced cancer patients
- Accelerate enrollment of partnered precision medicine clinical trials
- Catalyze new studies for patients harboring other targetable alterations

Objectives

Primary Objective

- Evaluate the proportion of subjects with genetic alterations targeted by approved or investigational therapies

Secondary Objectives

- Evaluate the proportion of subjects whose targeted genetic sequencing affected treatment selection and/or clinical trial enrollment
- Demonstrate the feasibility of a broad-based screening study of subjects utilizing molecular profiling and disseminating the results for relevant therapeutic protocols

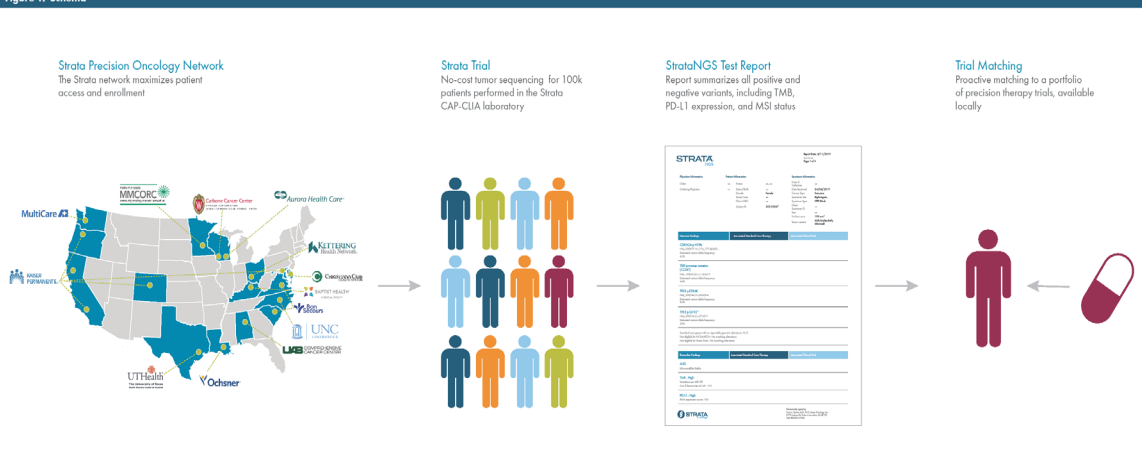
Exploratory Objective

- Determine the frequency of genetic alterations in subjects and explore potential relationships among genetic alterations and disease progression or treatment response

Methods

No-cost NGS testing is provided to a network of partnered centers within the Strata Precision Oncology Network. The archival FFPE tissue is submitted for NGS to Strata Oncology, a CLIA/CAP certified and NCI-MATCH accredited lab. The StrataNGS™ assay sequences DNA and RNA, and simultaneously assesses all classes of actionable genomic alterations including gene mutations, small insertions and deletions, copy number changes, and gene fusions in 500 cancer-related genes. Immunotherapy biomarkers include tumor mutational burden (TMB), PD-L1 expression, and microsatellite instability (MSI) status. MSI is determined via the number of length variant alleles observed in NGS sequencing data at several microsatellite loci. Test reports presented to the clinician include all positive and negative variants detected, and information about potential matching therapeutic protocols.

Figure 1. Schema

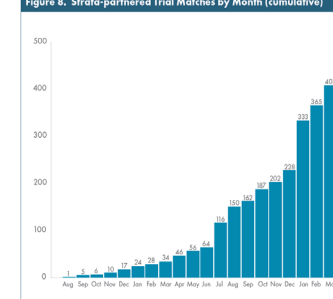


- Patients with advanced or metastatic cancer are eligible for testing. An archival FFPE tumor sample is shipped to the Strata Oncology CAP-certified, CLIA approved laboratory for no-cost tumor sequencing.
- A clinical report detailing tumor mutations and if applicable, a matching clinical trial, is returned to the provider in <10 d.
- For patients with a matching trial, the provider screens the patient for additional eligibility criteria and may consent and enroll the patient on the protocol.

Discussion

Through the implementation of streamlined consent methods, electronic medical record queries, and high throughput laboratory testing at no cost to patients, we demonstrate that scaled precision oncology is feasible across a diverse network of healthcare systems when paired with access to relevant clinical trials. Since the Strata Trial protocol encourages physicians to enroll and test subjects early to support improved decision making, it is not surprising that almost 70% of subjects are still being followed for potential enrollment into clinical trials. To date, 15% of patients that matched to locally available Strata-partnered therapeutic trials have been enrolled. The median time-to-enrollment from match to receipt of therapy was 6 months, with several patients enrolling 12+ months following identification. Since 89% of the matched patients were identified within 1 year of this analysis, and time to progression must be considered to accurately assess how many patients will eventually enroll, additional follow-up time is needed to better understand screen failure rates and clinical trial enrollment timelines. (Figure 8 – histogram) When assessing patients identified at least 1 year prior to this analysis, 35% of patients matched to locally available Strata-partnered trials have enrolled.

Figure 8. Strata-partnered Trial Matches by Month (cumulative)



Conclusions

- StrataNGS is capable of sequencing samples otherwise rejected by other available tests with short turnaround time to support eligibility assessment for targeted therapies
 - 52.4% of specimens received and successfully sequenced by Strata were < 25min*
 - StrataNGS minimum specimen size requirement = 2mm*
- Additional follow-up time is required to assess eligibility of patients recently matched to Strata-partnered therapeutic trials.

Results

StrataNGS Test Performance

Across the network of 17 active centers, specimens from 11334/12013 (94.3%) patients were successfully tested. 394 specimens were received with a quantity not sufficient for sequencing (QNS rate 3.3%). Median surface area of received FFPE tumor samples was 20mm² (interquartile range 8–90mm²), and the median turnaround time from sample receipt to report was 6 business days. (Figure 2; Figure 3).

Figure 2. Real-world Samples Received by Tumor Surface Area

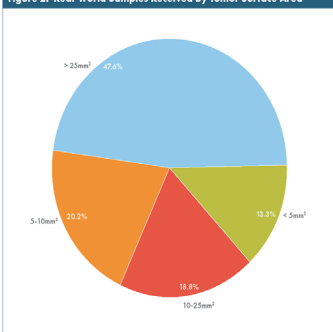


Figure 3. Turnaround Time (business days)

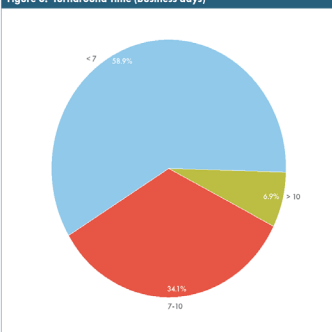
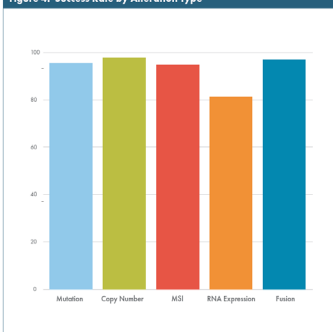


Figure 4. Success Rate by Alteration Type



Clinical Actionability

3600 (31.7%) patients had highly actionable alterations, defined as alterations associated with within cancer type FDA approved or NCCN guideline recommended therapies (1485 patients), NCI-MATCH trial arms (1636 patients), Strata-partnered therapeutic trials (408 patients), or specific alteration-matched FDA approved therapies in patients with cancers of unknown primary (71 patients). (Figure 5; Figure 6) Of the 1636 patients matched to an NCI-MATCH trial arm, 15 enrolled. Of the 408 patients matched to one of nine Strata-partnered clinical trials, 118 (29%) were screen failures, while 290 (71%) have either enrolled or are being actively followed for enrollment upon progression. (Figure 7).

Figure 5. Clinical Actionability

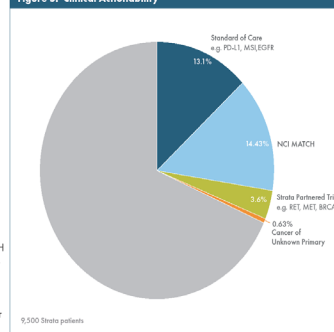


Figure 6. Distribution of Strata Partnered Trial Matches

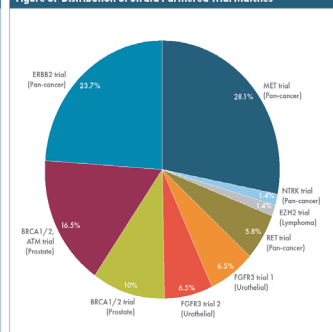
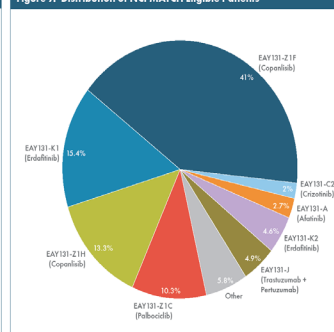
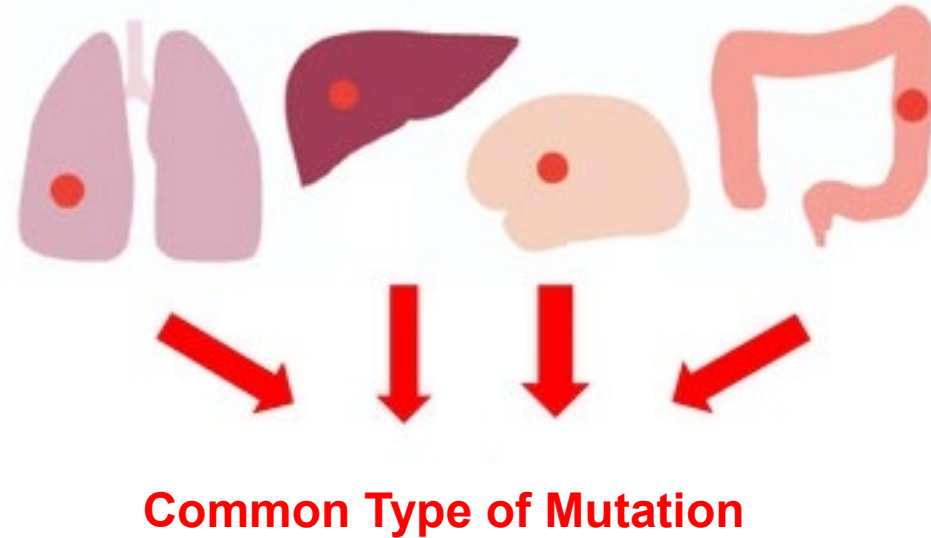


Figure 7. Distribution of NCI-MATCH Eligible Patients



Tumor Agnostic Precision Medicine

- Underlying driver mutations may be more important in defining some cancers than tissues of origin or type of cancer.



- Examples: HER2, NTRK, RET, BRAF, TMB, MSI-H, etc.

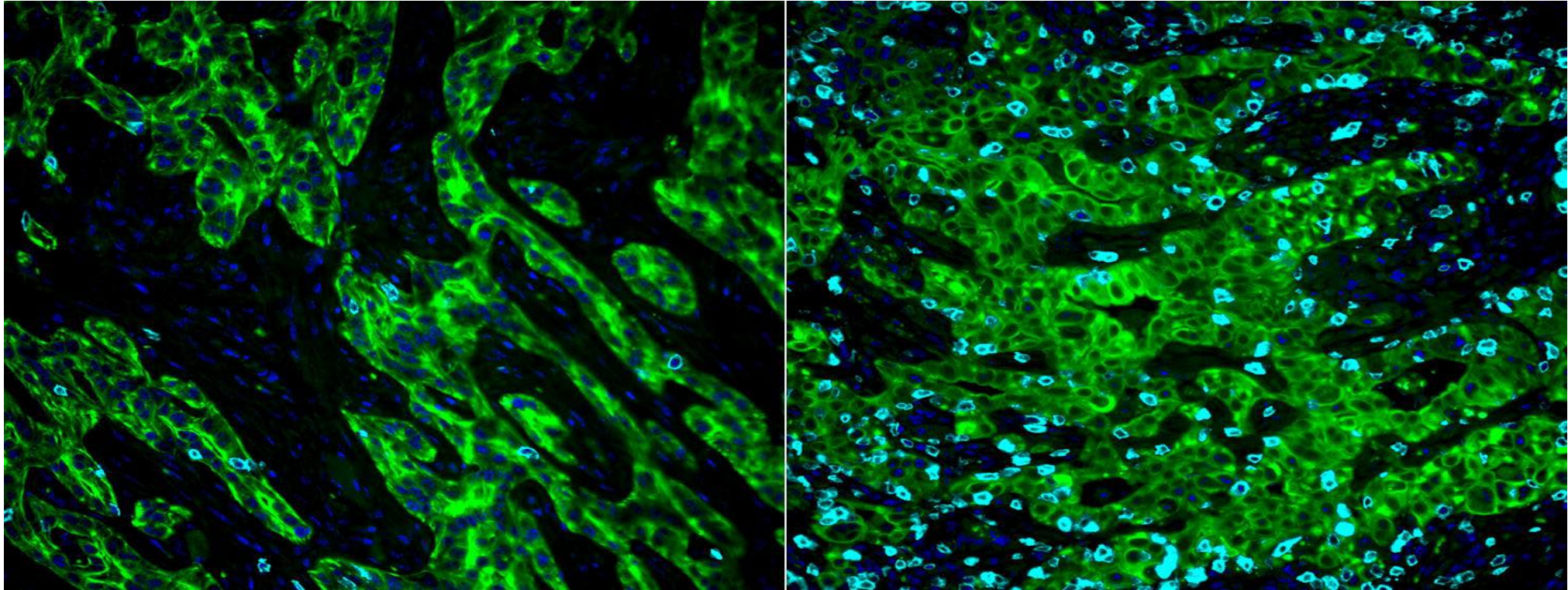
Next Generation Sequencing - Challenges

- May provide information which is difficult to act upon:
 - Mutation for which no drug targets
 - Actionable drug pair which has not been studied in the tumor type tested
 - Difficult to distinguish driver vs passenger mutations
 - Must consider tumor heterogeneity and tumor evolution
 - Insurance issues

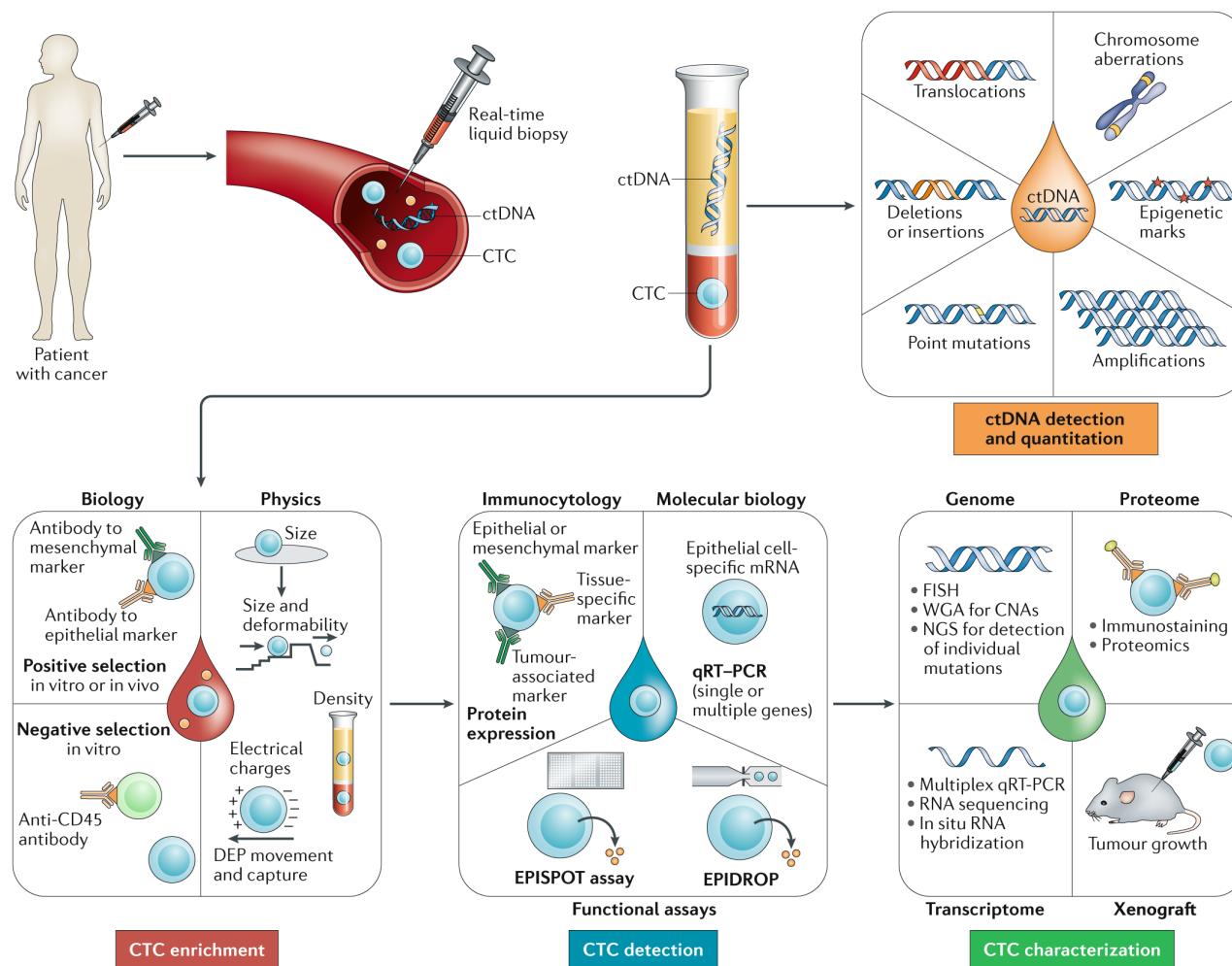
State-wide Molecular Tumor Board

- Currently held monthly with our molecular pathologists, physicians (surgeons, oncologists, etc.), LSU-Shreveport faculty, scientists from Strata NGS, fellows, research nurses, etc.
- We strongly welcome participation of any interested healthcare providers.
- E-mail Nicole Perry: nicole.perry@ochsner.org

Minimal Residual Disease Testing



MRD in Solid Tumors



MRD for Recurrence Monitoring

- Commercially available (Natera Signatera, Guardant Reveal, etc.), but limited clinical studies to guide clinical decisions with positive tests (i.e., start therapy, etc.).
- Unclear how often to test, etc.

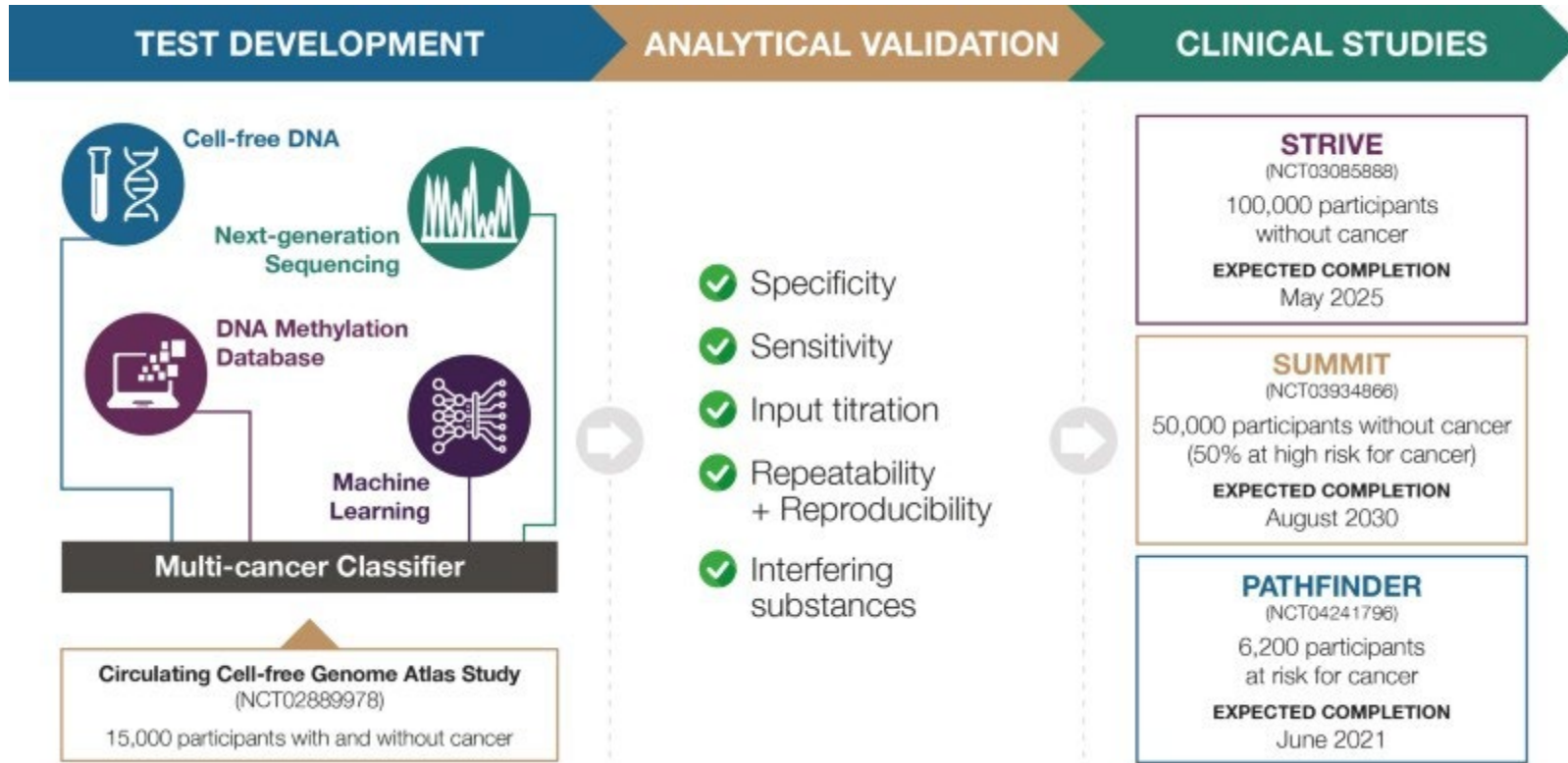
MRD for Response Monitoring

- Emerging area for Precision Medicine.
 - Circulating tumor DNA as a tool to monitor response to therapy.
 - May be particularly useful for Stage IV pts undergoing non-curative treatments.

Multi-Cancer Early Detection



Genomic Screening for Cancer



Multi-Cancer Early Detection: Blood-Based Screening

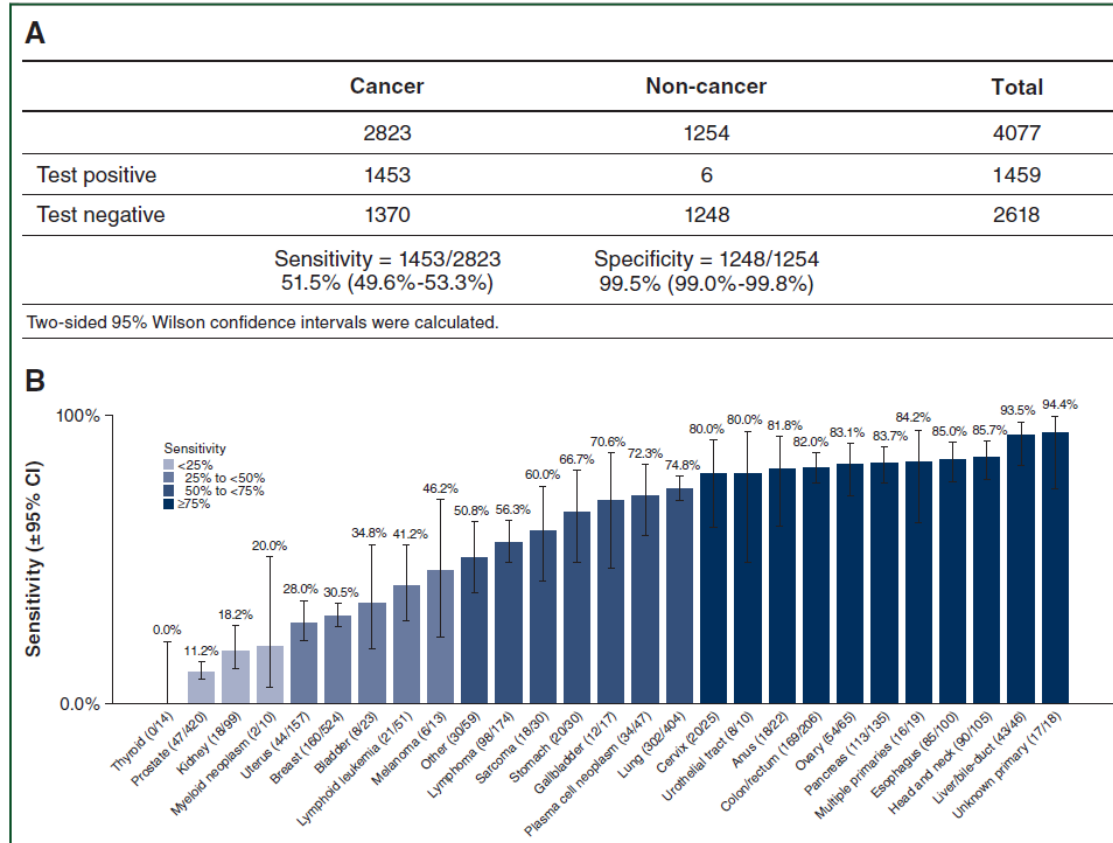


Figure 3. MCED test performance for cancer signal detection (A) overall sensitivity and specificity, (B) sensitivity by cancer class, and (C) sensitivity by stage in 12 pre-specified cancers. (A) The 2 × 2 contingency table summarizes overall sensitivity and specificity. (B) Sensitivity (y-axis) by cancer class based on individual cancer classes (x-axis), including other, unknown primary, and multiple primaries. Cancer classes are ordered based on increasing sensitivity; bars indicate 95% CI. (C) Sensitivity by stage is depicted in each box for each of the 12 pre-specified cancer classes; bars indicate 95% CI. CI, confidence interval; MCED, multi-cancer early detection.

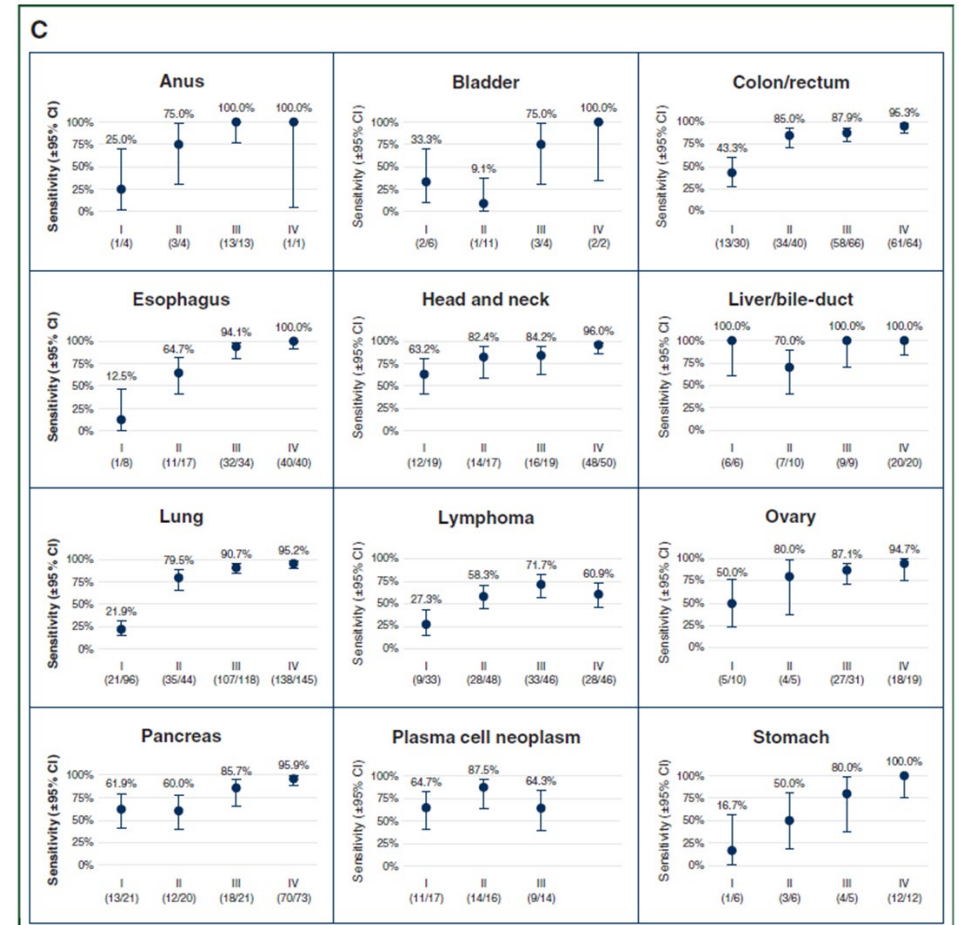


Figure 3. Continued.

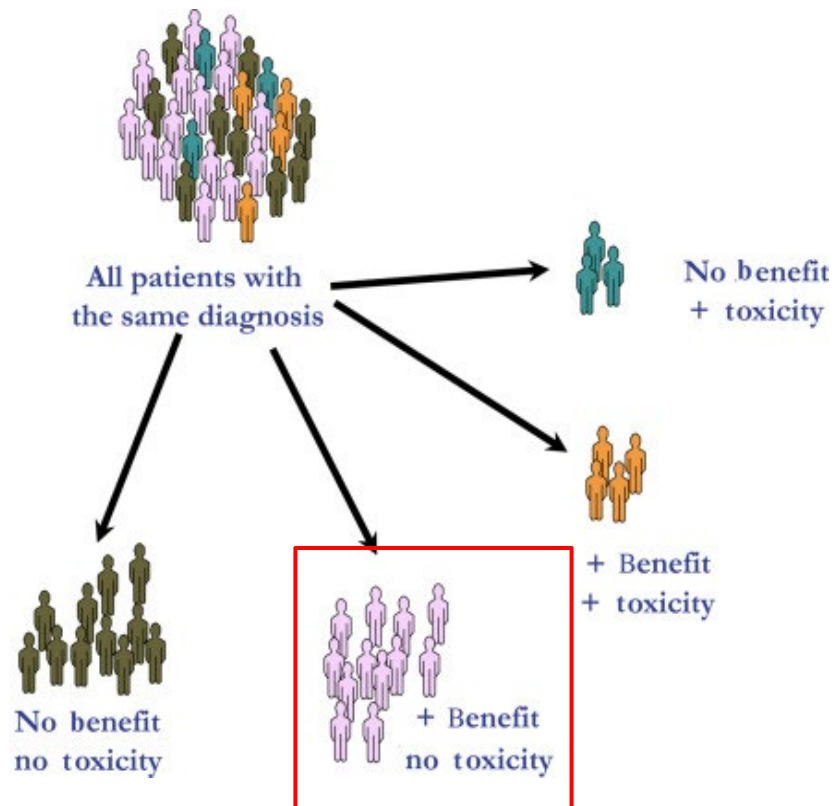
Pharmacogenomics



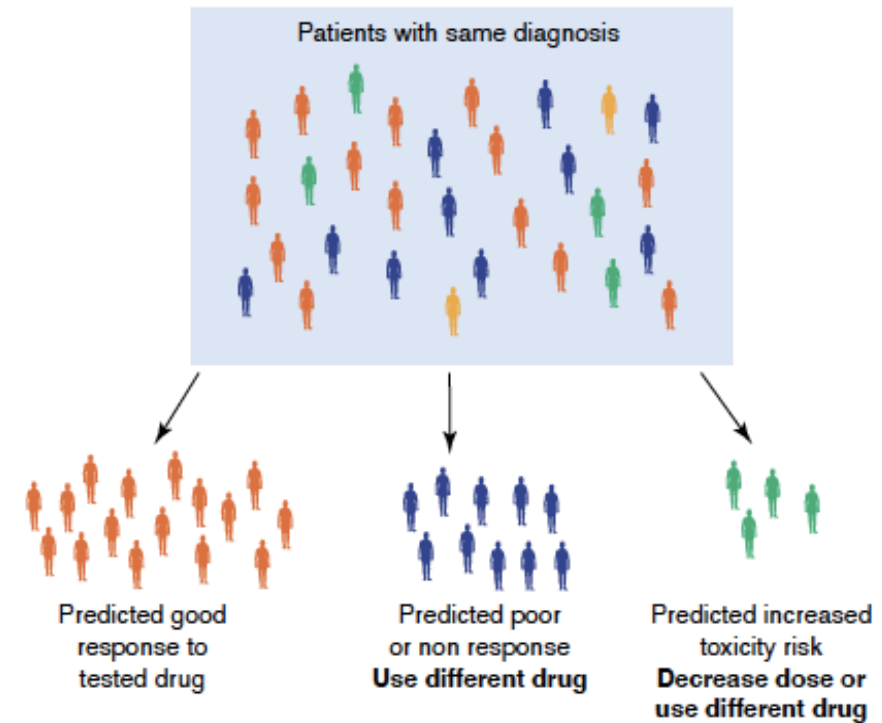
What is Pharmacogenomics (PGx)?

- For clinicians – using knowledge of genetic changes in metabolic enzymes, drug transporters, and drug receptors to guide medication selection
- For patients – understanding that changes in their DNA may affect the way the process or react to medication

Current State



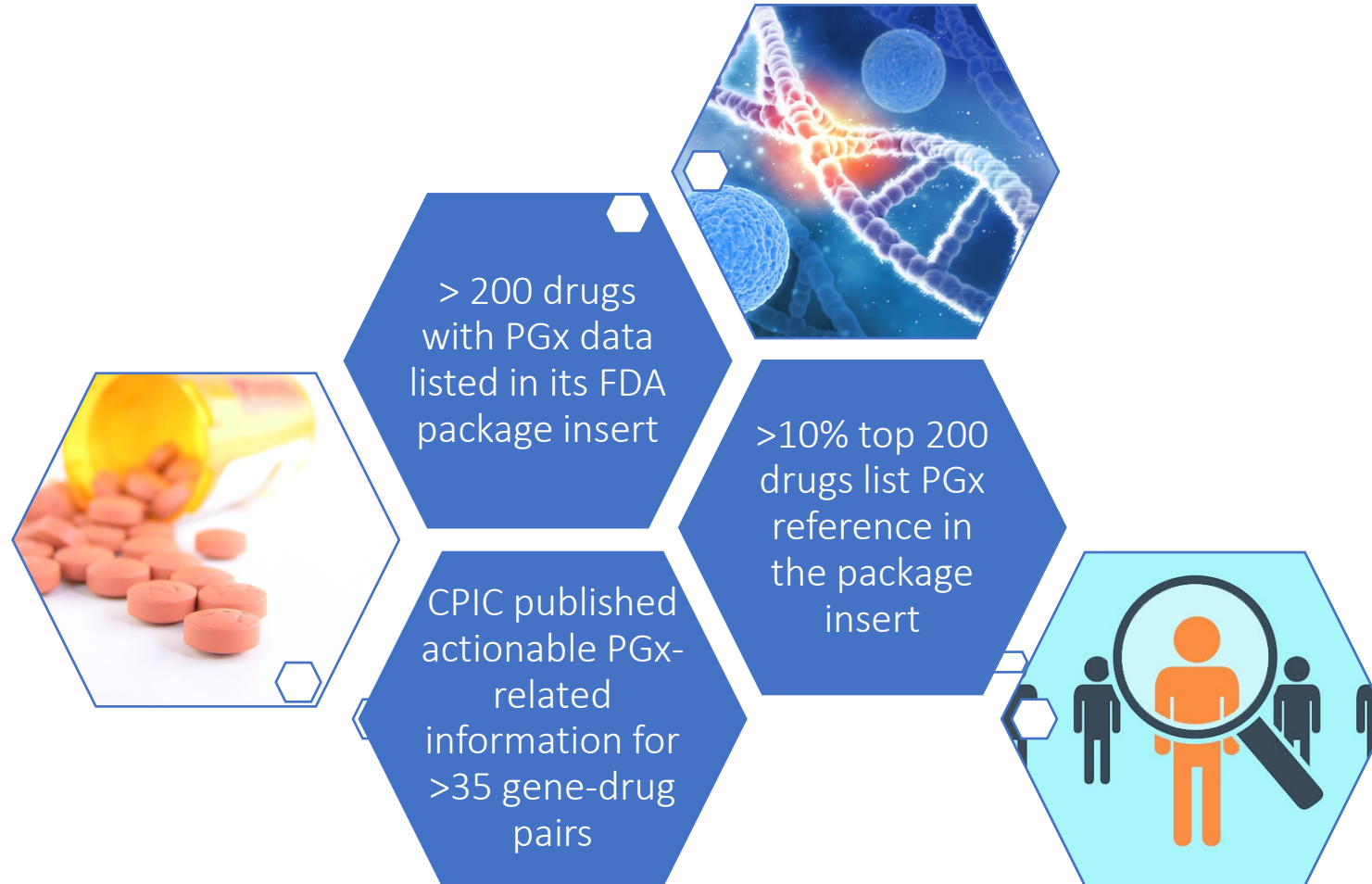
Future State



Allows for more personalized approach to drug utilization

TRENDS in Genetics

The Medications



Pharmacogenomics: Prevalence of Actionable Variants

99%

Patients carried at least ONE actionable pharmacogene variant



- Based on study performed on 7,769,359 US Veterans Health Administration (VHA) patients who use the VHA pharmacy services



>50%

Of pharmacy population has been exposed to a drug affected by these variants

Among the VHA pharmacy patients:

- 54.8% received at least 1 level A drug
- 15.3% received 2 drugs
- 11.7% received 3 or more

Therapeutic Areas

Current CPIC Guidelines for Drug-Gene Pairs

Cardiology

- Clopidogrel – *CYP2C19*
- Simvastatin – *SLCO1B1*
- Warfarin – *CYP2C9* and *VKORC1*

Infectious Disease

- Abacavir – *HLA-B*57:01*
- Atazanavir – *UGT1A1*
- PEG-interferon – *IL28B*
- Efavirenz - *CYP2B6*
- Voriconazole - *CYP2C19*
- AMGs - *MT-RNR1*

Neurology

- Carbamazepine – *HLA-B*15:02*
- Phenytoin – *CYP2C9, HLA-B*15:02*
- Atomoxetine - *CYP2D6*

Oncology

- Thiopurines – *TPMT*
- Capecitabine/5-FU – *DPYD*
- Rasburicase – *G6PD*
- Tamoxifen - *CYP2D6*

Pain Management

- Codeine – *CYP2D6*
- Tramadol – *CYP2D6*
- Tricyclic antidepressants – *CYP2C19, CYP2D6*
- NSAIDs - *CYP2C9*

Psychiatry

- Tricyclic antidepressants – *CYP2C19, CYP2D6*
- Selective serotonin reuptake inhibitors – *CYP2C19, CYP2D6*

Rheumatology

- Thiopurines – *TPMT, NUDT15*
- Allopurinol – *HLA-B*58:01*

Solid Organ Transplant

- Tacrolimus – *CYP3A5*



Respiratory

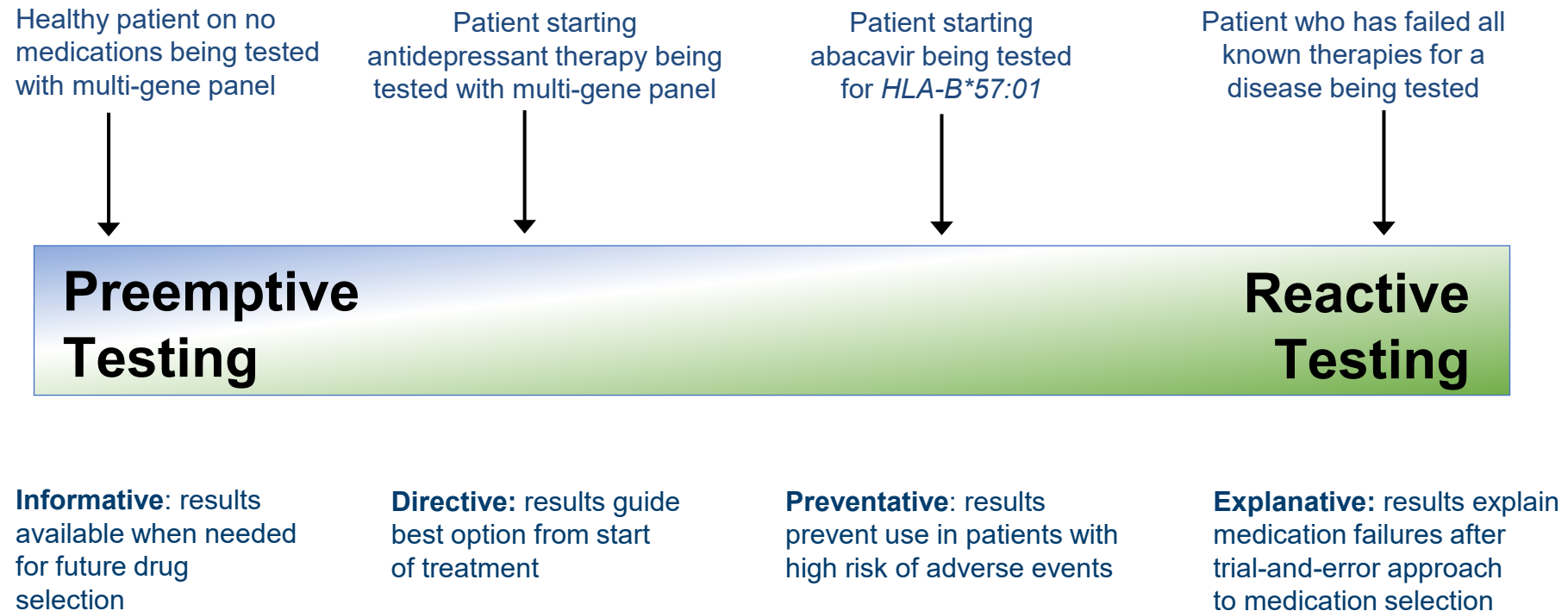
- Ivacaftor – *CFTR*

Other

- PPI – *CYP2C19*
- Ondansetron - *CYP2D6*
- Anesthesia - *RYR1, CACNA1S*

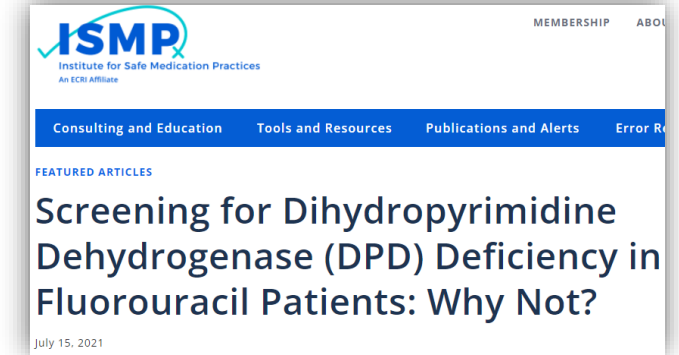


Timing of PGx test and change in value



Required DPYD Testing at Ochsner

- Cost of Screening: Medicare/Medicaid Covered, Avg OOP <\$90
- Delay in Therapy: ~5-day T-A-T
- Lack of Consensus on Dosing: CPIC Guidelines
- Decreased Efficacy in Cancer Treatment: PK studies
- NCCN does not endorse: BUT Acknowledges feasibility



Ochsner Experience:

- January 2020 – May 2021: 106 patients were tested for DPYD genetic variation in reaction to adverse events related to 5-fluorouracil or capecitabine therapy
- 11 patients tested positive for at least one mutation with clinically significant variation in drug metabolism
- 8 patients had potentially avoidable consequences if pre-emptively tested

Oregon Health System Settles Chemotherapy Death Lawsuit

July 16, 2022



CATEGORIES

Select Category ▼

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Oregon Health System Settles Chemotherapy Death Lawsuit: Oregon Health & Science University ("OHSU") reportedly has agreed to pay \$1 million to the widow of a cancer patient who allegedly died as a result of a toxic reaction to a chemotherapy drug due to a genetic variant that affects about 8% of the population. OHSU reportedly also agreed as part of the settlement that its oncologists will advise patients about the genetic variant before initiating the chemotherapy drug capecitabine.



HEALTHCARE & PHARMACEUTICALS FEBRUARY 15, 2021 / 5:26 PM / UPDATED 2 YEARS AGO

Bristol-Myers, Sanofi ordered to pay Hawaii \$834 million over Plavix warning label

By Tina Bellon, Nate Raymond

2 MIN READ



(Reuters) - A judge in Hawaii on Monday ordered Bristol-Myers Squibb Co and Sanofi SA to pay more than \$834 million to the state for failing to warn non-white patients properly of health risks from its blood thinner Plavix.



BPA Alerts: Critical Interaction Interruptive Alerts


Any drug-gene-phenotype interaction with a PGx contradiction for use or recommendation to dose reduce related to the following:

- Risk of SJS, TEN, other SCAR
- Risk of severe neutropenia, thrombocytopenia, myelosuppression
- PGx-related black box warning
- Treatment failures => risk of uncontrolled pain, vomiting, fungal infection or organ rejection

BestPractice Advisory - Beacon, Bacon


Critical (1)

Pharmacogenomic Interaction - CYP2D6 Ultrarapid Metabolizer / Ondansetron


 INCREASED RISK of therapeutic failure/poor response due to low plasma concentrations of ondansetron. **Select an ALTERNATIVE medication not extensively metabolized by CYP2D6, such as granisetron.**

For questions, call 504-703-GENE (4363) or order PGx Consult [CON227].

Remove the following orders?

 ondansetron (ZOFRAN-ODT) 8 MG TbDL
Take 1 tablet (8 mg total) by mouth in the morning and 1 tablet (8 mg total) before bedtime.
Normal

Apply the following?

 PGx Consult

[Review this patient's genomic indicators](#)

Acknowledge Reason

- Risk of acute hemolytic anemia
- Increased risk of other SAEs: severe respiratory depression, hepatotoxicity, QT events, visual disturbances
- PGx label contraindication and on FDA Table of Pharmacogenetic Associations

Inline Alert – Significant Interactions

Drug-gene-phenotype interactions with PGx recommendations to:

- **Avoid use**
 - Select alternate treatment to decrease risk of adverse events or treatment failure
- **Reduce dose**
 - Dose reduce to offset increased risk of adverse events due to predicted increases in drug plasma concentrations

codeine 15 MG Tab ✓ Accept ✗ Cancel

⚠ Pharmacogenomic Warning

CYP2D6 Ultrarapid Metabolizer / Codeine: INCREASED RISK of toxicity as codeine is too rapidly converted to morphine. Select an ALTERNATIVE analgesic agent. If opioid use is warranted, avoid tramadol. For questions, call 504-703-GENE (4363) or order PGx Consult (CON227).

Reference Links: 1. [Dose Adjustments](#) 2. [Micromedex](#)

Order Inst.: [Opioid Risk Tool Score](#) [None](#) (TOOL NOT COMPLETED) [Current Potential Daily Morphine Equivalence = 0 mg MEDD](#)

⚠ I have reviewed the Prescription Drug Monitoring Program (PDMP) database for this patient prior to prescribing the above opioid medication

Yes No

Product: **CODEINE SULFATE 15 MG ORAL TAB** [View Available Strengths](#)

Sig Method: **Specify Dose, Route, Frequency** [Use Free Text](#) [Taper/Ramp](#) [Combination Dosage](#)

Dose: mg **15 mg** [30 mg](#) [60 mg](#)

Prescribed Dose: 15 mg
Prescribed Amount: 1 tablet
Maximum MME/Day: 13.5 MME/Day for this order (13.5 MME/Day for signed and unsigned orders)

Route:

⚠ Frequency: **Q4H PRN** [Q6H PRN](#)

PGx Support

- Epic Clinical Decision Support tools available – Providers DO NOT have to be proactive
- Pharmacy PGx Consult is available
 - Epic: PharmacoGENOMICS Consult Order (CON227)
- Or Contact Info:
 - Phone: (504) 703-GENE (4363)
 - Email: PGx@Ochnser.org

Whole Genome Sequencing



Rapid WGS in NICU

Project Baby Bear – 178 Infants Tested

[FINAL REPORT LINK](#)

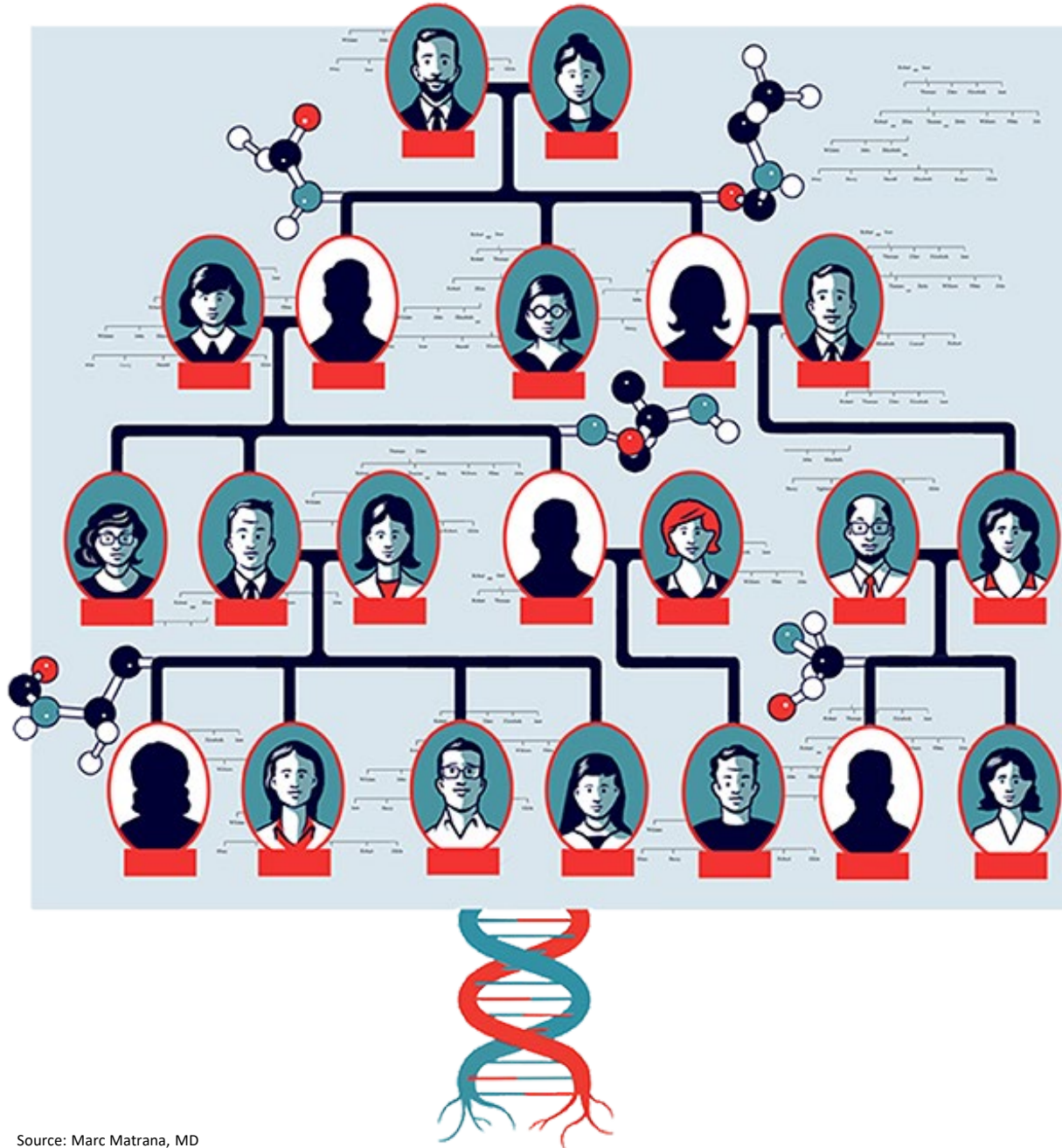
Better Outcomes: For Baby, Family, and Clinicians

- **FASTER**- Identified the cause in three days instead of 4-6 WEEKS
- **BETTER**– 43% with a specific diagnosis; 31% adjustment in medical management
- **CHEAPER** – \$2.5M reduction in spending through fewer hospital days and reduced procedures
- ***The outcome motivated CA Legislation to expand coverage

Ochsner Pediatric Genetics

- 6 week old patient presented with Hypertrophic Cardiomyopathy
- Patients <6mo have a 60-70% mortality rate
- Patient placed on heart transplant candidacy list
- Genetic testing identified a genetic marker, allowing for targeted treatment with Trametinib
- Patient is now 2 years old with a positive outlook and no longer on heart transplant list!

Hereditary Screening

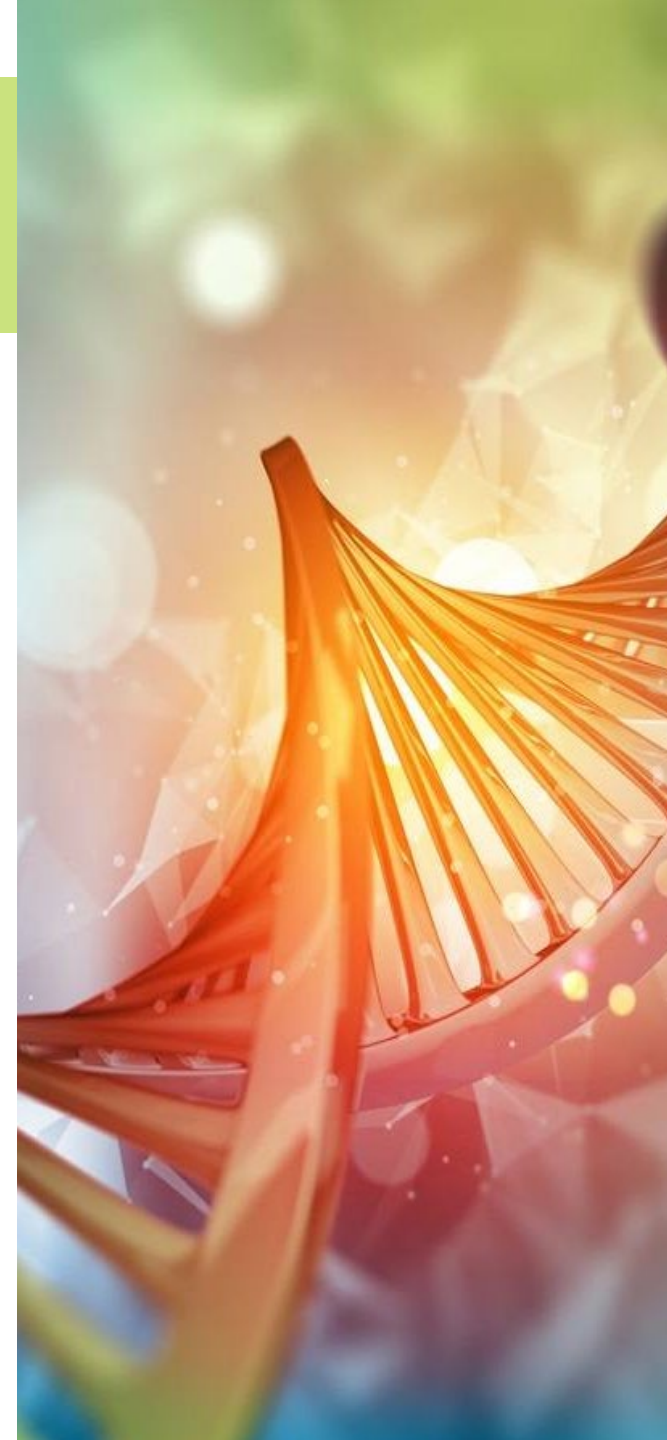
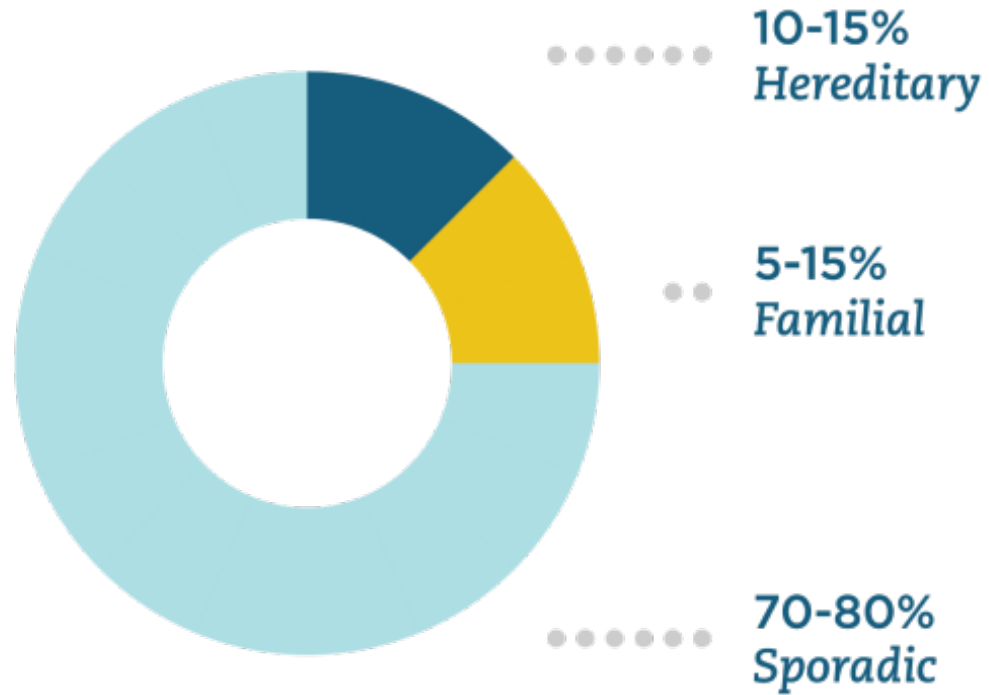


Having certain inherited gene mutations can increase a patient's risk for certain types of cancer.

Understanding a patient's mutational status and risk allows us to better tailor screening and prevention strategies.

Genetic counselors can help patients and families navigate and better understand complex genetics scenarios.

Hereditary Cancer Risks



The Future *is* Precision Medicine



- What Does the Future Hold?
 - Precision and Molecular Medicine will transform every aspect of medical care
 - Adoption of new technologies (CRISPR, gene editing, etc), germline?
 - Greater integration of other “-omics”
 - Expansion and refinement of AI and advanced machine learning
 - Expanded access, lower prices
 - Better science = better outcomes for patients





**ANY
QUESTIONS?**

