Combining Germline and Somatic Pharmacogenomics for Comprehensive Cancer Care

Clinical applications of pharmacogenomics for patients with cancer

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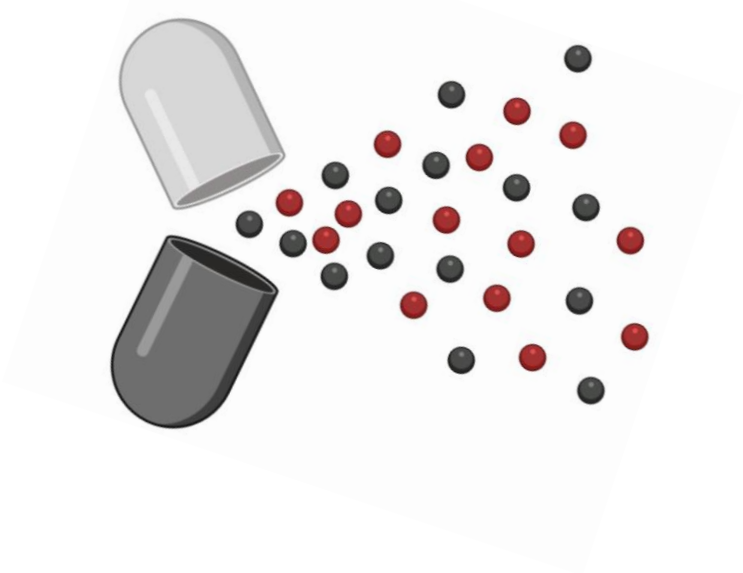
Contents

What Is Pharmacogenomics (PGx)?

Pharmaco(logy)

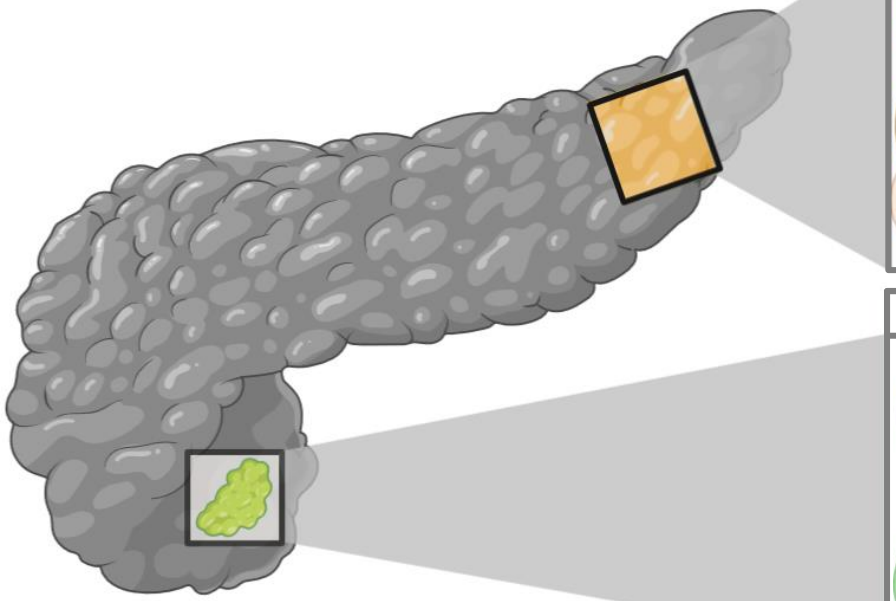
The science of how drugs work in the body

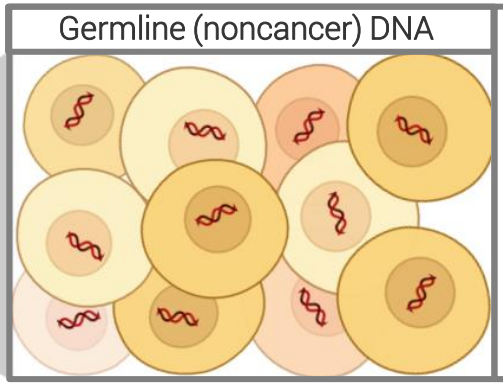


The science of how genes work in the body

Genomics

Two Main PGx Categories

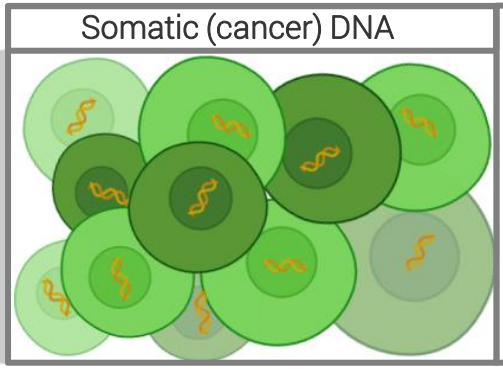




Germline PGx:

Testing genes from cells in the body that are inherited/passed on

(noncancerous cells/DNA/RNA)

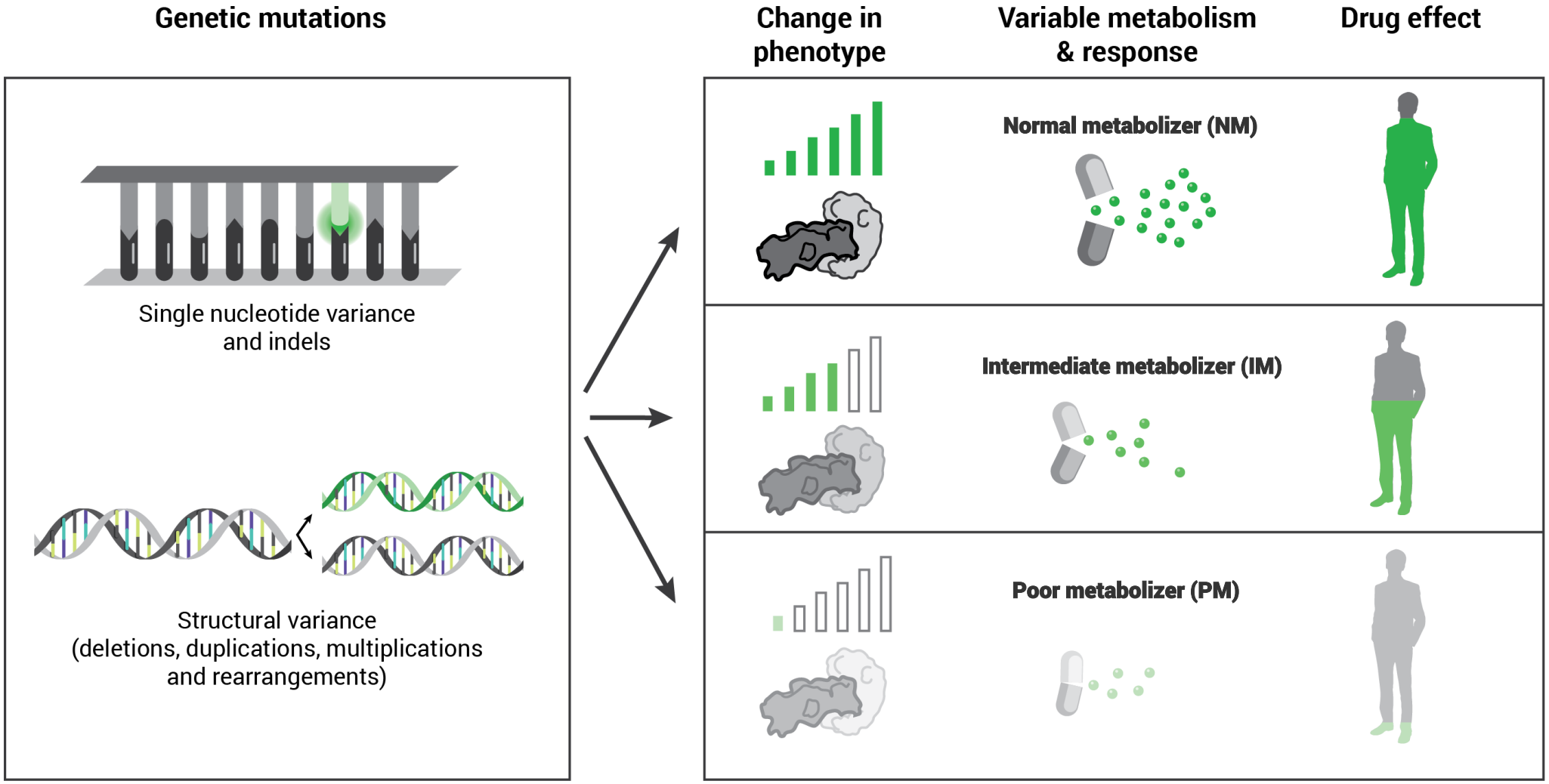


Somatic PGx:

Testing genes from cells in the body that aren't inherited/passed on

(cancer cells/DNA/RNA)

Germline PGx



Why Should We Care About PGx?

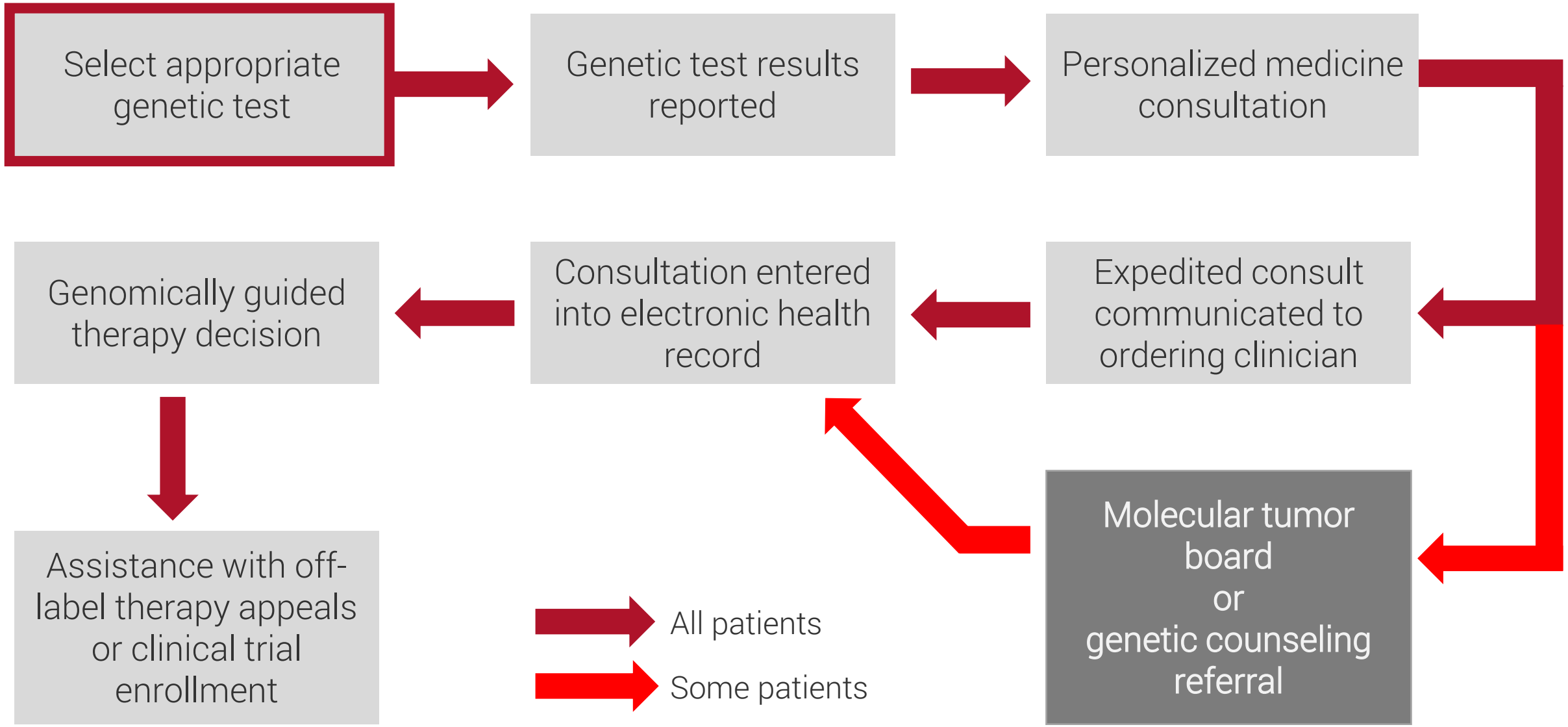
- Medications and therapies can provide numerous BENEFITS:
  - » Extend life
  - » Improve quality of life in patients with cancer

- However, there is also a risk of inherent UNTOWARD EFFECTS:
  - » Unsuccessful cancer treatment, unresolved depression, untreated pain, unsuccessful fungal infection prevention/treatment, etc.
  - » Severe (sometimes lethal) adverse effects/reactions

Why Should We Care About PGx?

- Prioritizes best possible care for our patients
- Minimizes adverse drug effects
- Reduces unnecessary spending on hospitalizations
- Avoids repeat clinician visits from therapy failure
- Avoids potentially ineffective cancer therapies (if mutation is absent)

Clinical Workflow



Patient Case

John is a 45-year-old male with stage IV, unresectable pancreatic adenocarcinoma metastatic to the liver, who was originally diagnosed 2 weeks ago.

Previous treatment:	None
Planned treatment:	FOLFIRINOX (FOLnic acid, Fluorouracil, IRINotecan, OXaliplatin)
Other medications:	Paroxetine, tramadol, ondansetron (among other meds)

As part of a risk mitigation strategy, a **germline variant panel** was ordered.

****This patient case will be the same case used longitudinally throughout the presentation, but clinical context will be added as the presentation progresses.****

Selecting a Germline PGx Panel

Planned treatment:

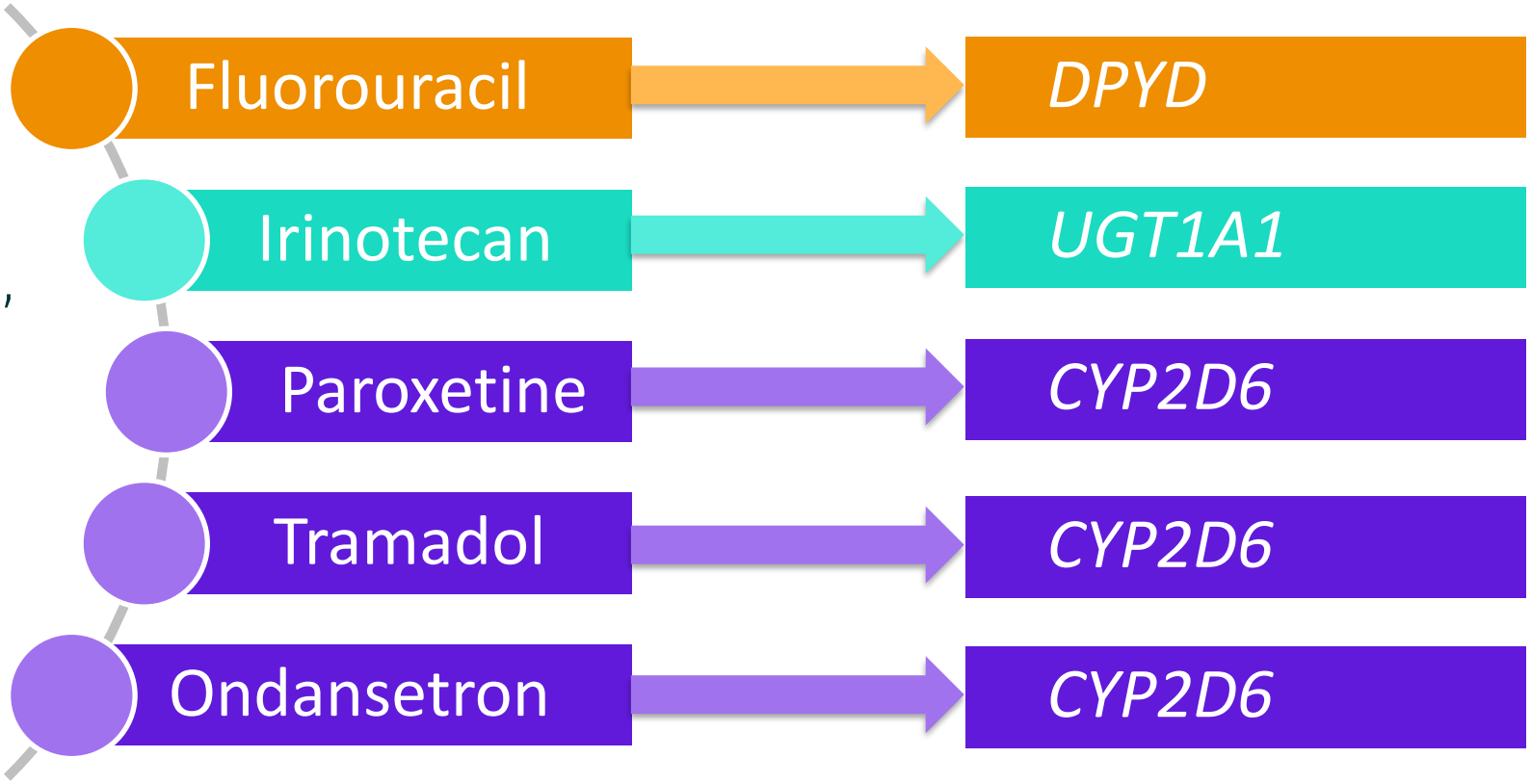
- FOLFIRINOX

(FOLinic acid, Fluorouracil, IRINotecan, OXaliplatin)

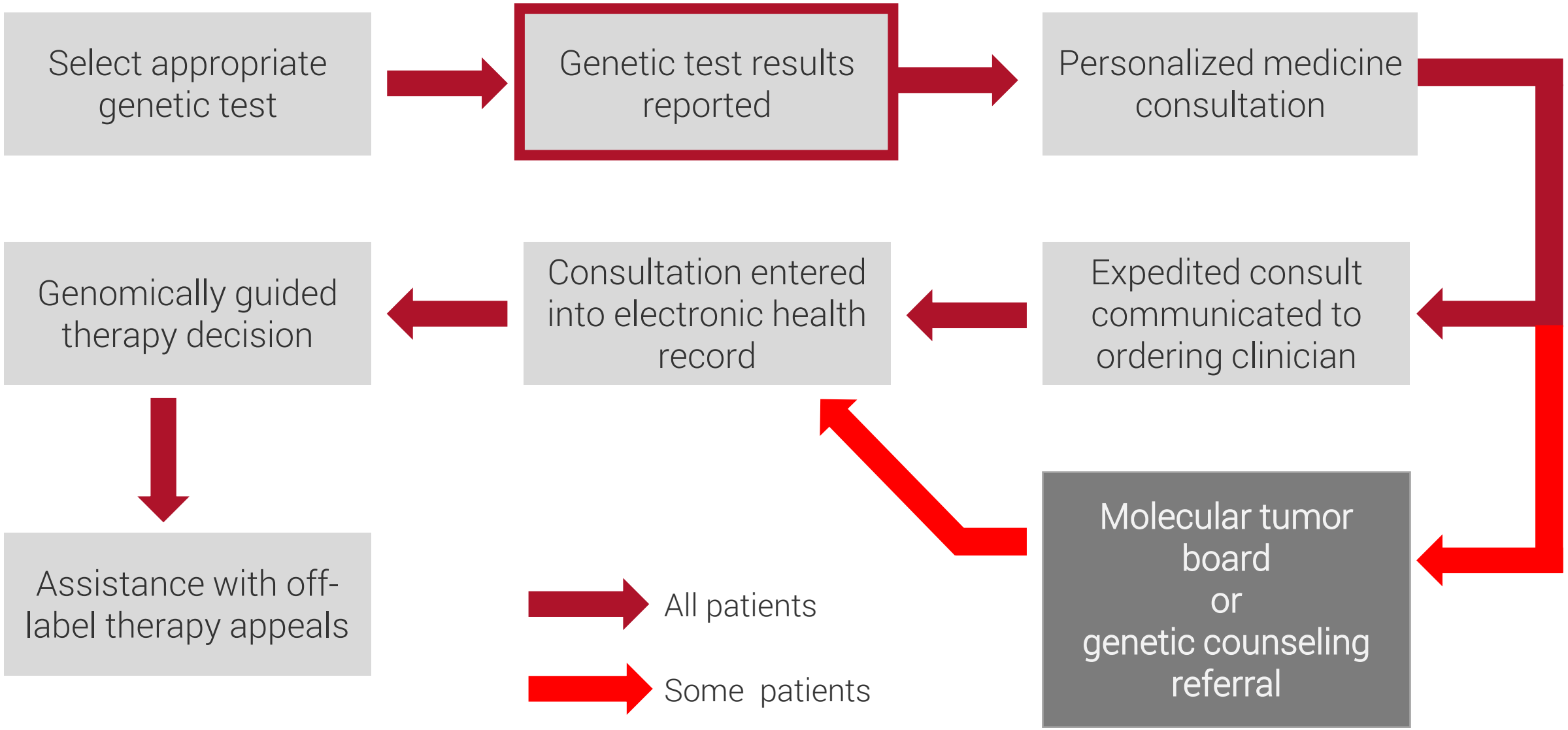
Other medications:

- Paroxetine, tramadol, ondansetron

(among other meds)



Clinical Workflow



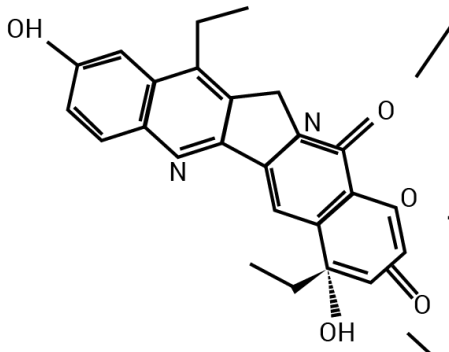
Germline PGx Panel Findings

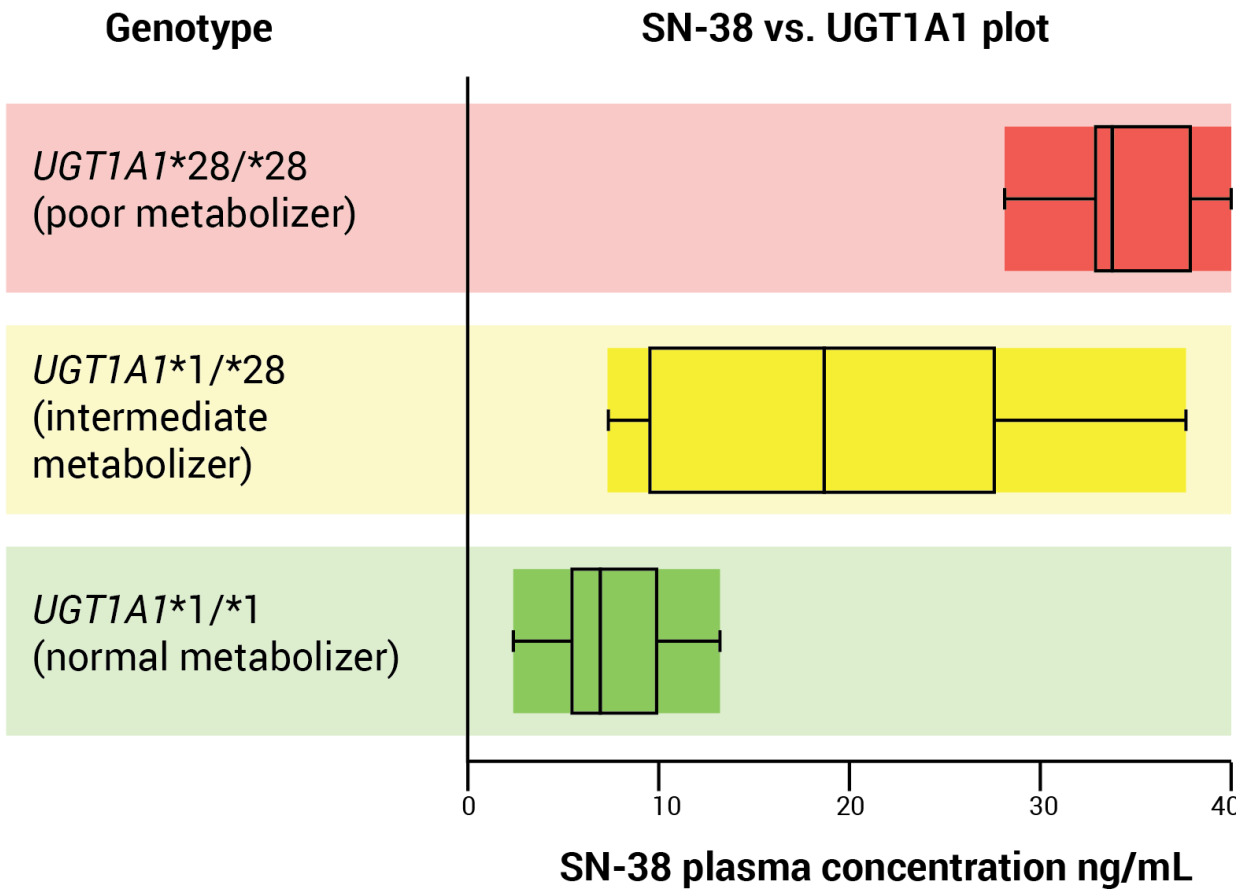
- Before beginning FOLFIRINOX, John's medical oncologist was provided with numerous treatment recommendations based on three reported germline variants
- Pertinent findings are as follows:

UGT1A1 PGx

- Irinotecan is bioactivated to SN-38: responsible for efficacy and toxicity
- UGT1A1 is involved in glucuronidation of endogenous and exogenous substances
- *UGT1A1*28* and **6* cause reduced UGT1A1 expression and SN-38 glucuronidation
- Increased SN-38 can cause severe neutropenia and diarrhea

Irinotecan (inactive) + **Carboxylesterases** → **SN-38 (active metabolite)**





Patient Case (continued)

John was found to have:

- One wild-type allele (**1*) and
  one decreased-function allele (**28*)

- *UGT1A1 *1/*28* =
  UGT1A1 IM

https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf
CAMPTOSAR Drug Label, 2020

PGx-Based Recommendations for Irinotecan

Comparison of PGx Recommendations Between Guideline and Administrative Authorities		
	Topic, Artifact, or Statement	Irinotecan
CPIC	CPIC level	A
	CPIC clinical recommendations	NR
FDA	PGx associations with sufficient evidence to allow their use in guiding therapy management	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (severe neutropenia). Consider reducing the starting dosage by one level and modify the dosage based on individual patient tolerance for **28/*28* (PMs).
	Associations with data to suggest a potential impact on drug safety or response	NR
	Associations with data demonstrating only an impact on pharmacokinetic properties	NR
DPWG	Recommendations	*UGT1A1 *1/*28*: No action is needed for this gene-drug interaction. *UGT1A1 *28/*28*: Start with 70% of the standard dose. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
NCCN	Recommendations	Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. Guidelines for use in clinical practice have not been established.
EMA	Recommendations	An initial dose reduction from 80 to 60 mg/m^2 is recommended in patients with *UGT1A1 *28/*28* (PMs).

https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf, CAMPTOSAR Drug Label, 2020, https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/pharmacogenomics-working-party, https://www.nccn.org, https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

UGT1A1 Clinical Decision Support

Irinotecan Dosing Recommendations Based on *UGT1A1* Genotype/Phenotype[a]			
UGT1A1 Result	UGT1A1 Phenotype	Implications	Dosing Recommendations
**1/*1*	Normal metabolizer	No influence on SN-38 plasma concentrations	Consider usual irinotecan dosage and titrate based on response
**1/*6* **1/*28*	Intermediate metabolizer	Risk of toxicity due to elevated SN-38 plasma concentrations	Consider usual irinotecan dosage and titrate based on response
**6/*6* **6/*28* **28/*28*	Poor metabolizer	Risk of toxicity due to elevated SN-38 plasma concentrations	For irinotecan doses ≥250 mg/m^2, consider a 30% reduction of the usual starting dosage and titrate based on response For irinotecan doses <250 mg/m^2, consider the usual irinotecan dosage and titrate based on response The FDA drug label provides additional guidance for drug dosing
[a]Weight, liver function, previous irinotecan exposure, and other patient characteristics may influence drug selection and dosage.			

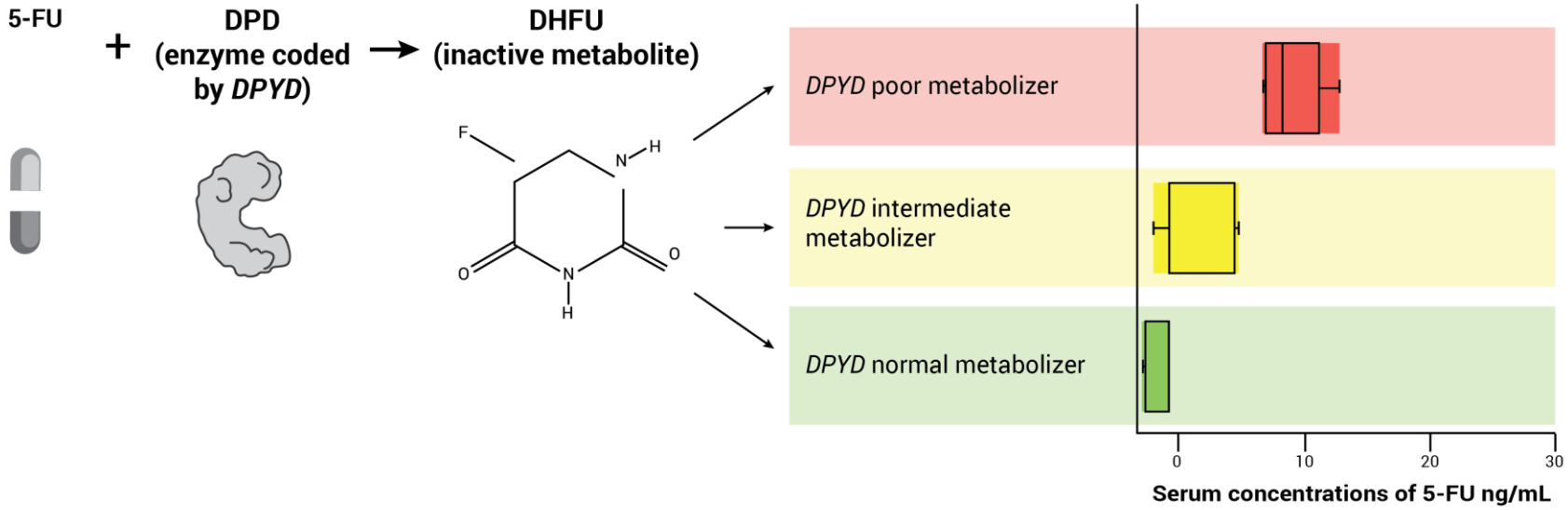
https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf

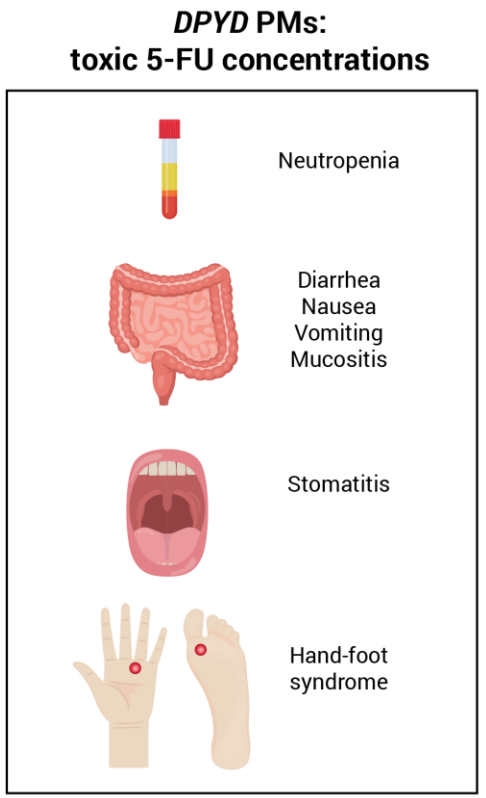
Germline PGx Panel Findings

- Before beginning FOLFIRINOX, John's medical oncologist was provided with numerous treatment recommendations based on three reported germline variants
- Pertinent findings are as follows:

DPYD PGx

- *DPYD*, the gene encoding dihydropyrimidine dehydrogenase (DPD), is the rate-limiting enzyme for fluoropyrimidine catabolism (e.g., 5-FU)
- Capecitabine and 5-FU are widely used drugs for the treatment of gastrointestinal malignancies (and others)
- Between 10% and 40% of patients develop severe toxicity (neutropenia, nausea, vomiting, severe diarrhea, stomatitis, mucositis, hand-foot syndrome)





Clin Pharmacol Ther. 2018 Feb;103(2):210-216.

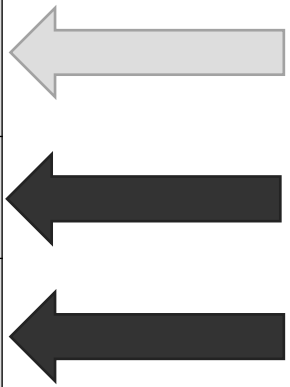
DPYD PGx

- *DPYD *1/*2A*
- John was found to have one wild-type allele (**1*) and one no-function allele (**2A*)
- Clinical guidelines recommend a prophylactic 50% 5-FU dose reduction for John

Clin Pharmacol Ther. 2018 Feb;103(2):210-216
Lancet Oncol. 2018 Nov;19(11):1459-1467

PGx-Based Dosing Applied Chemotherapy

Dosing Adjustments Implemented in the FOLFIRINOX Regimen		
Drug	Standard Dose (Unadjusted)	PGx-Based Dose (% Reduction)
Irinotecan	180 mg/m^2	180 mg/m^2 (no reduction)
5-FU bolus	400 mg/m^2	200 mg/m^2 (50% reduction)
5-FU continuous infusion	2,400 mg/m^2 (over 2 days)	1,200 mg/m^2 (50% reduction)
Leucovorin	400 mg/m^2	900 mg
Oxaliplatin	85 mg/m^2	190 mg



Front Pharmacol. 2018; 9:1309

Germline PGx Panel Findings

- Before beginning FOLFIRINOX, John's medical oncologist was provided numerous treatment recommendations based on three reported germline variants
- Pertinent findings are as follows:

CYP2D6 PGx

- Responsible for metabolism of ~15-25% of all clinically used drugs
- Responsible (in part) for the metabolism of:
  - » Tramadol: bioactivation of O-desmethyltramadol (200-fold greater affinity for μ-opioid receptors than the parent drug)
  - » Ondansetron: increased metabolism of parent drug (influencing antiemetic effect)
  - » Paroxetine: increased metabolism of parent drug (impacting plasma concentrations and potential therapy failure)

CYP2D6 Metabolic Activity Scores

Functional Status	Activity Score	Alleles
Increased function	>1	**1xN, *2xN, *35xN, *45xN*
Normal or increased function	1 or >1	**9xN, *17xN, *29xN, *41xN*
Normal function	1	**1, *2, *27, *33, *34, *35, *39, *45, *46, *48, *53*
Decreased function	0.5	**9, *14B, *17, *29, *41, *49, *50, *54, *55, *59, *72, *84*
Decreased function	0.25	**10*
No function	0	**3, *3xN, *4, *4xN, *5, *6, *6xN, *7, *8, *11, *12, *13, *14A, *15, *18, *19, *20, *21, *31, *36, *36xN, *38, *40, *42, *44, *47, *51, *56, *57, *62,*68, *69, *92, *96, *99, *100, *101*

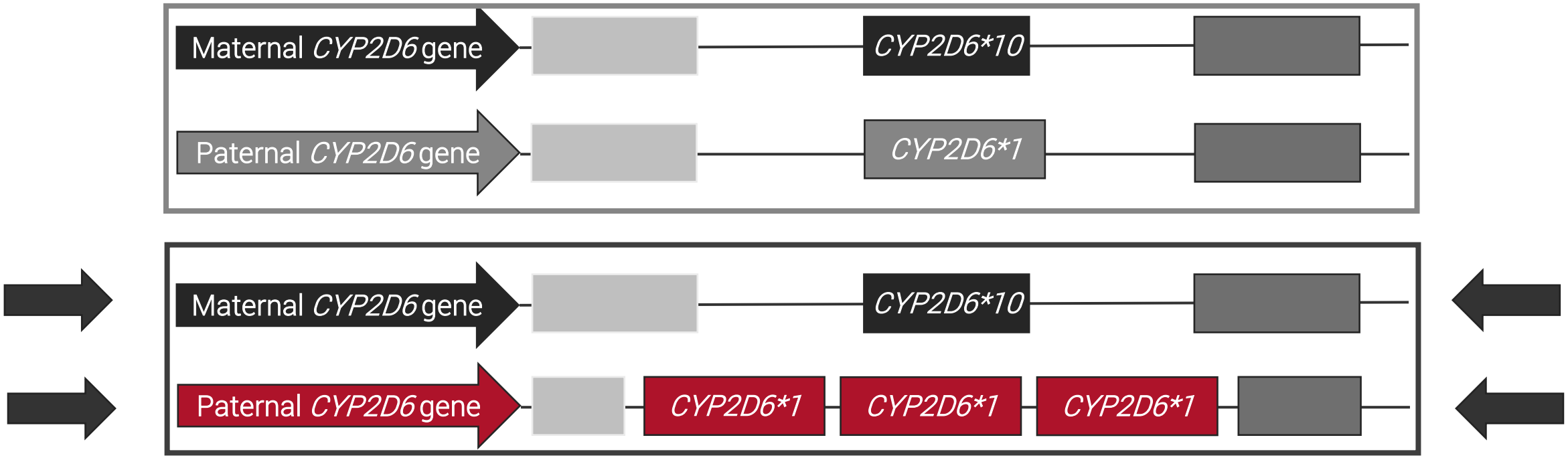
Clin Transl Sci. 2020 Jan; 13(1): 116–124

CYP2D6 Predicted Phenotype

Phenotype	Activity Score	Proposed % Activity[a]	Description
Ultrarapid metabolizer (UM)	**>2.25**	**>110**	Individual carrying more than two copies of functional alleles
Normal metabolizer (NM)	**1.25-2.25**	**75-110**	Individual carrying two alleles encoding full or reduced function, or one full-function allele together with either one functional or one reduced-function allele
Intermediate metabolizer (IM)	**0.25-1**	**10-74**	Individual carrying one reduced-function and one nonfunctional allele
Poor metabolizer (PM)	**0**	**0-9**	Individual carrying no functional alleles

[a]Proposed % activity is not to be considered a precise defined range but rather an approximation to illustrate the spectrum of activity scores.
Table adapted from Table 3 and Figure 3 of Clin Transl Sci. 2020 Jan; 13(1): 116–124

CYP2D6 Polymorphisms

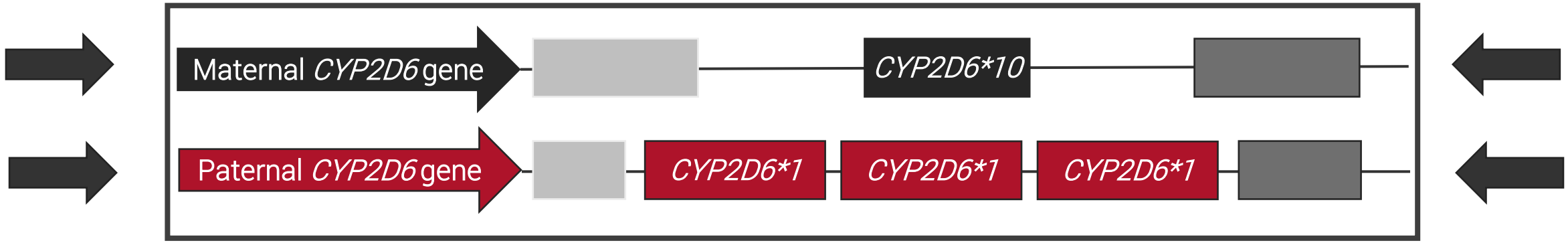


Some humans have more than two copies of *CYP2D6*

- This can lead to increased *CYP2D6* metabolic activity
- In this case, the phenotype would be a UM

Koch WH. Nat Rev Drug Discov. 2004 Sep;3(9):749-61

CYP2D6 Polymorphisms



Some labs do not report allele-specific copy numbers for *CYP2D6*

- This can lead to ambiguous *CYP2D6* metabolic activity
  - *CYP2D6 (*1/*10) 4N*
  - *CYP2D6 (*1/*10) N*
  - *CYP2D6 *1/*10(3N)*
  - ***CYP2D6 *1(3N)/*10***

Ambiguity here can lead to risk of misinterpreting phenotypic predictions and affect therapeutic decisions

Koch WH. Nat Rev Drug Discov. 2004 Sep;3(9):749-61

Variability in Predicted *CYP2D6* Phenotypes

- *CYP2D6* activity scores can vary depending on how the genes are tested and analyzed
- Ensuring *CYP2D6* allele-specific duplication reporting can be provided is essential
- Risk of misreporting predicted phenotypes:
  - » UM as an NM
  - » IM as a PM

SNV data alone			SNV + structural variation data		
Diplotype	**AS**	**n**	**Diplotype**	**AS**	**n**
Deletion					
**1/*1*	2	39	**1/*5*	↓ 1	8
**2/*2*	2	9	**2/*5*	↓ 1	4
**35/*35*	2	2	**5/*35*	↓ 1	1
**41/*41*	1	5	**5/*41*	↓ 0.5	4
**4/*10*	0.5	3	**4/*5*	↓ 0	1
**3/*3*	0	1	**3/*5*	→ 0	1
**4/*4*	0	17	**4/*5*	→ 0	4
Duplication					
**1/*1*	2	39	**1/*1x2*	↑ 3	1
**1/*2*	2	36	**1x2/*2*	↑ 3	1
**2/*35*	2	3	**2x2/*35*	↑ 3	1
**2/*41*	1.5	16	**2x2/*41*	↑ 2.5	1
**1/*4*	1	41	**1x2/*4*	↑ 2	1
**2/*4*	1	19	**2x2/*4*	↑ 2	1
**10/*41*	1	1	**10/*41x2*	↑ 1.5	1

Clinical and Translational Science, Volume: 13, Issue: 1, Pages: 147-156, First published: 19 September 2019, DOI: (10.1111/cts.12695)

CYP2D6 PGx Applied to John

- *CYP2D6* *1 *(3N)/* *10* = UM
  - » Tramadol: increased bioactivation of O-desmethyltramadol (opioid toxicity risk)
  - » Ondansetron: increased metabolism of parent drug (reducing antiemetic effect)
  - » Paroxetine: increased metabolism of parent drug (unsuccessful depression treatment)

https://cpicpgx.org/genes-drugs/
https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf

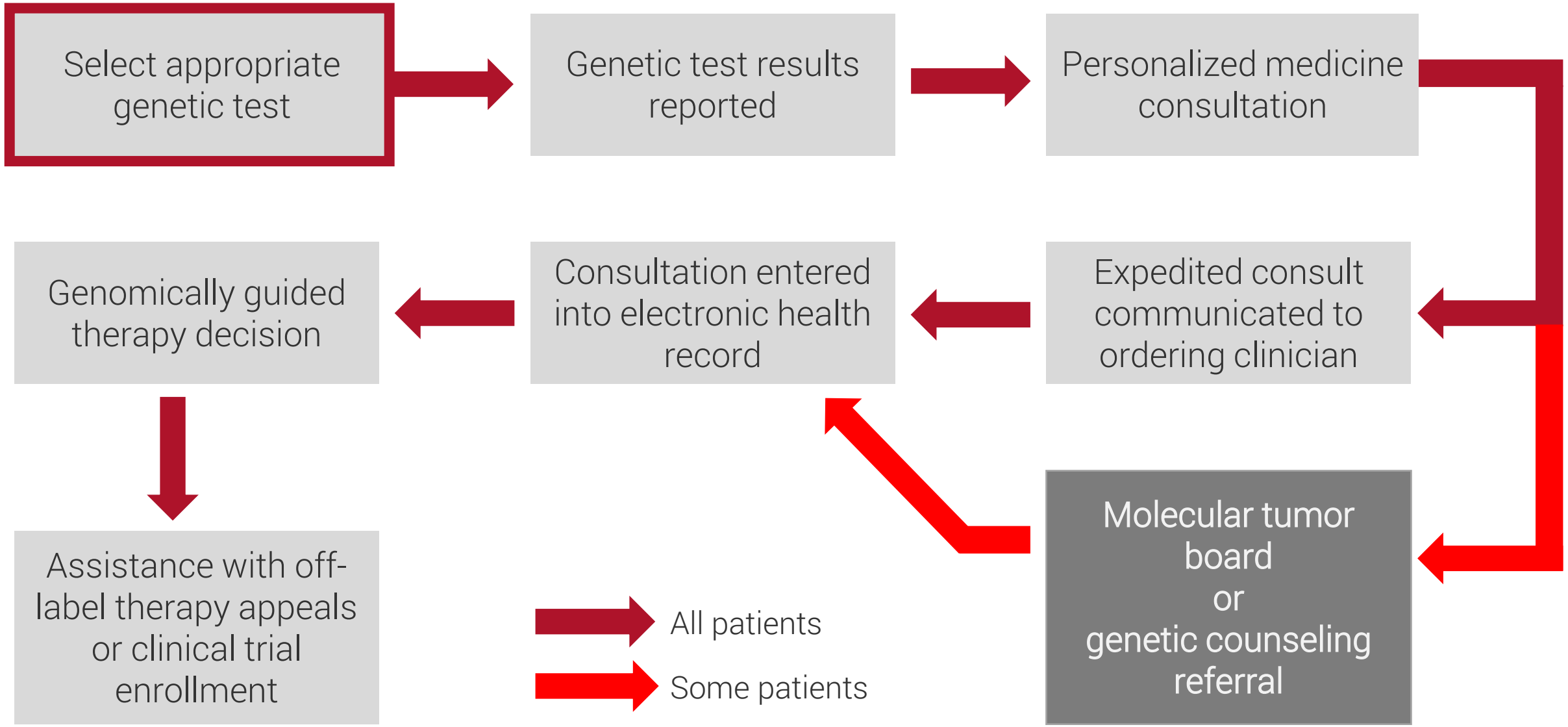
Germline PGx Summary Points

- Germline PGx tests the noncancer DNA
- Genetic variance can lead to variability in effect/toxicity to medications and therapies, sometimes leading to severe toxicity and lethality
- Not all germline PGx testing platforms are the same; knowing what genes and alleles they interrogate and how/if they report allele-specific copy number variance is essential

Patient Case (continued)

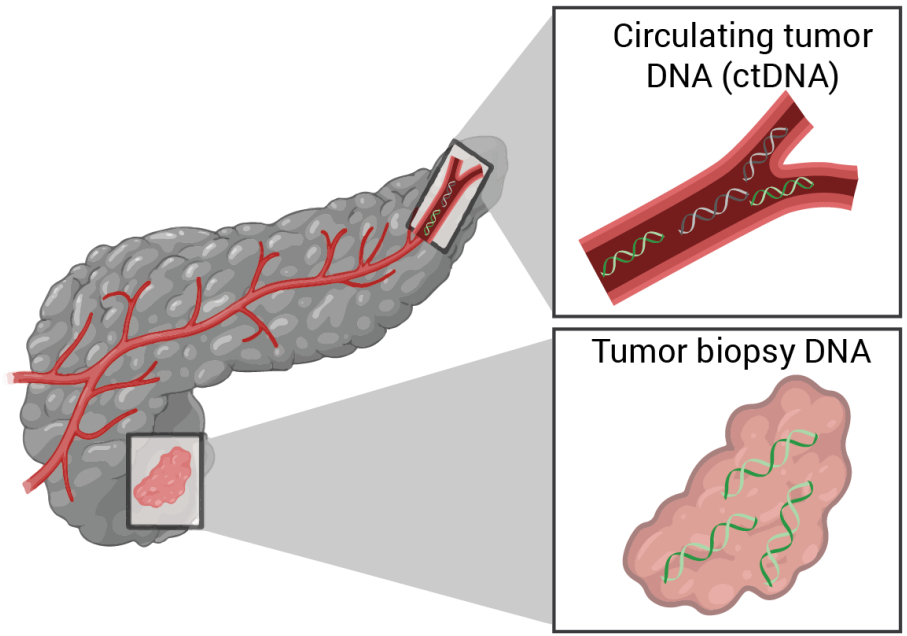
The physician knows they would like to order an NGS tumor panel but is undecided about which will be most appropriate for John

Clinical Workflow



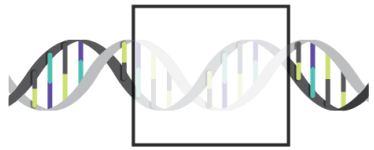
Somatic PGx

Somatic DNA sources



Genetic alteration types

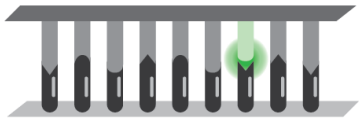
Gene deletions



Gene amplifications

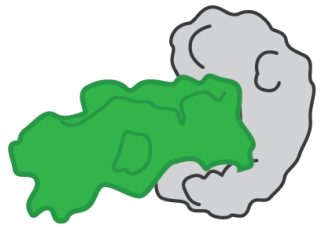
Gene fusions & translocations

Point mutations

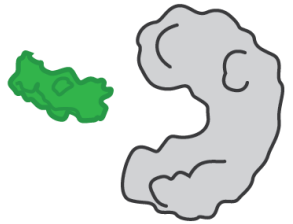


Functional outcomes

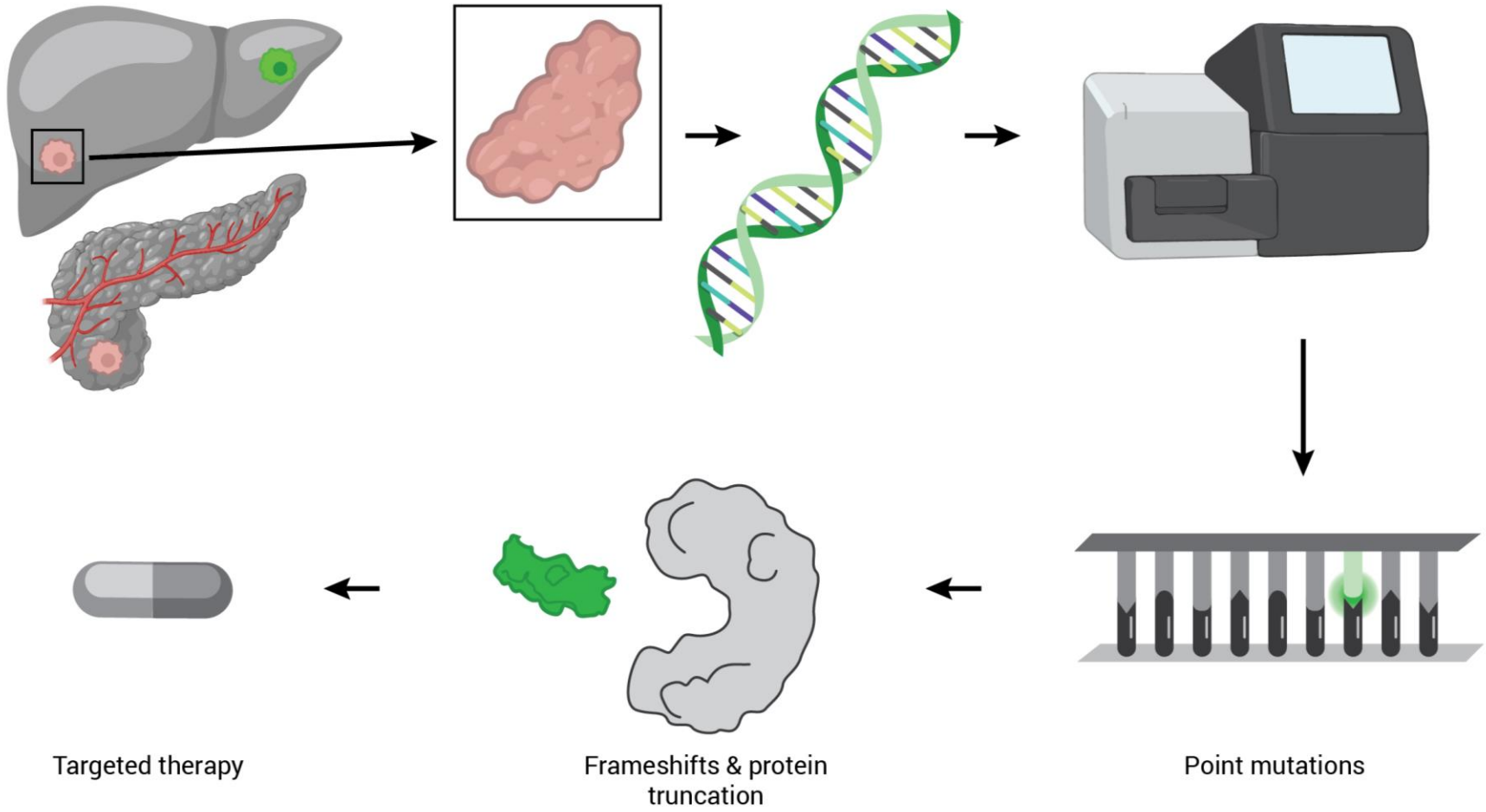
Protein expression, activation or inactivation



Frameshifts & protein truncation



Somatic Panel Workflow



Selecting an Appropriate Somatic Panel

- Selecting the appropriate somatic panel is important and must take the following into context:
  - » Cancer type, resectable vs. nonresectable tumor
  - » Point in therapeutic timeline (at recurrence or during therapy response)
    - If prior tissue is available, determining the likelihood of resistance mutations having developed after the time the biopsied sample was obtained
  - » Synchronous metastases
  - » Coverage of anticipated biomarkers for desired targeted therapy
    - RNA seq for reliable fusion detection
    - Microsatellite instability coverage
    - Tumor mutation burden

ctDNA Testing Platform Considerations

Advantages

No tissue biopsy needed

Reduced time, resources, and costs to acquire blood compared to tissue

Serial testing to follow clonal expansion or clearance of cancer cells over time

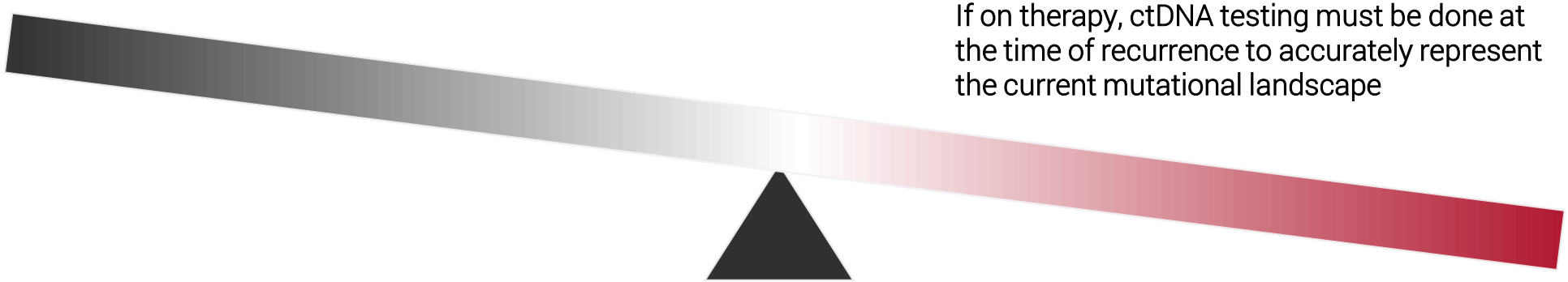
Able to detect alterations in primary and metastatic tumors in same sample

Challenges

Cases with low tumor burden or no detected mutations are difficult to interpret

Difficult to determine clonality in synchronous tumors

If on therapy, ctDNA testing must be done at the time of recurrence to accurately represent the current mutational landscape



CLINICAL CANCER RESEARCH

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Precision Medicine and Imaging

Circulating Tumor DNA Predicts Outcome from First-, but not Second-line Treatment and Identifies Melanoma Patients Who May Benefit from Combination Immunotherapy

Gabriela Marsavela, Jenny Lee, Leslie Calapre, Stephen Q. Wong, Michelle R. Pereira, Ashleigh C. McEvoy, Anna L. Reid, Cleo Robinson, Lydia Warburton, Afaf Abed, Muhammad A. Khattak, Tarek M. Meniawy, Sarah-Jane Dawson, Shahneen Sandhu, Matteo S. Carlino, Alexander M. Menzies, Richard A. Scolyer, Georgina V. Long, Benhur Amanuel, Michael Millward, Melanie R. Ziman, Helen Rizos, and Elin S. Gray

DOI: 10.1158/1078-0432.CCR-20-2251 Check for updates

ABSTRACT

Purpose: We evaluated the predictive value of pretreatment ctDNA to inform therapeutic outcomes in patients with metastatic melanoma relative to type and line of treatment.

Experimental Design: Plasma circulating tumor DNA (ctDNA) was quantified in 125 samples collected from 110 patients prior to commencing treatment with immune checkpoint inhibitors (ICIs), as first- ($n = 32$) or second-line ($n = 27$) regimens, or prior to commencing first-line BRAF/MEK inhibitor therapy ($n = 66$). An external validation cohort included 128 patients commencing ICI therapies in the first- ($N = 77$) or second-line ($N = 51$) settings.

Results: In the discovery cohort, low ctDNA (≤20 copies/mL) prior to commencing therapy predicted longer progression-free survival (PFS) in patients treated with first-line ICIs [HR, 0.20; 95% confidence interval (CI) 0.07–0.53; $P < 0.0001$], but not in the second-line setting. An independent cohort validated that ctDNA is predictive of PFS in the first-line setting (HR, 0.42; 95% CI, 0.22–0.83; $P = 0.006$), but not in the second-line ICI setting. Moreover, ctDNA prior to commencing ICI treatment was not predictive of PFS for patients pretreated with BRAF/MEK inhibitors in either the discovery or validation cohorts. Reduced PFS and overall survival were observed in patients with high ctDNA receiving anti–PD-1 monotherapy, relative to those treated with combination anti–CTLA-4/anti–PD-1 inhibitors.

Conclusions: Pretreatment ctDNA is a reliable indicator of patient outcome in the first-line ICI treatment setting, but not in the second-line ICI setting, especially in patients pretreated with BRAF/MEK inhibitors. Preliminary evidence indicated that treatment-naïve patients with high ctDNA may preferentially benefit from combined ICIs.

Translational Relevance

Low pretreatment plasma ctDNA level is predictive of longer progression-free survival in patients with melanoma receiving first-line immune checkpoint inhibitors, but its predictive value is lost in the second-line setting, particularly after treatment with BRAF ± MEK inhibitors. Patients with treatment-naïve melanoma with high pretreatment ctDNA levels showed a trend toward better outcomes when treated with combination anti–CTLA-4/anti–PD-1 ICIs rather than anti–PD-1 alone. Quantification of ctDNA may be useful for the stratification of patients who will likely benefit from combination immunotherapy.

Solid Tumor Panel Selected

illumina

TruSight™ Oncology 500 and TruSight Oncology 500 High-Throughput*

Enabling comprehensive genomic profiling from FFPE samples, with flexibility and scalability.

Highlights

- **Save time and sample with a multiplex assay**
  Comprehensive, pan-cancer content spanning 523 cancer-relevant genes aligned with key guidelines and clinical trials
- **Unlock immuno-oncology with TMB and MSI**
  1.94 Mb of content with sophisticated algorithms enable accurate analysis of TMB and MSI
- **Achieve confidence in results**
  Enrichment chemistry including UMIs coupled with an informatics pipeline for high accuracy in variant detection
- **Address the needs of the oncology community both today and tomorrow**
  Relevant and emerging biomarkers support a future-proof foundation for new solutions

One workflow for multiple tumor types and multiple biomarkers

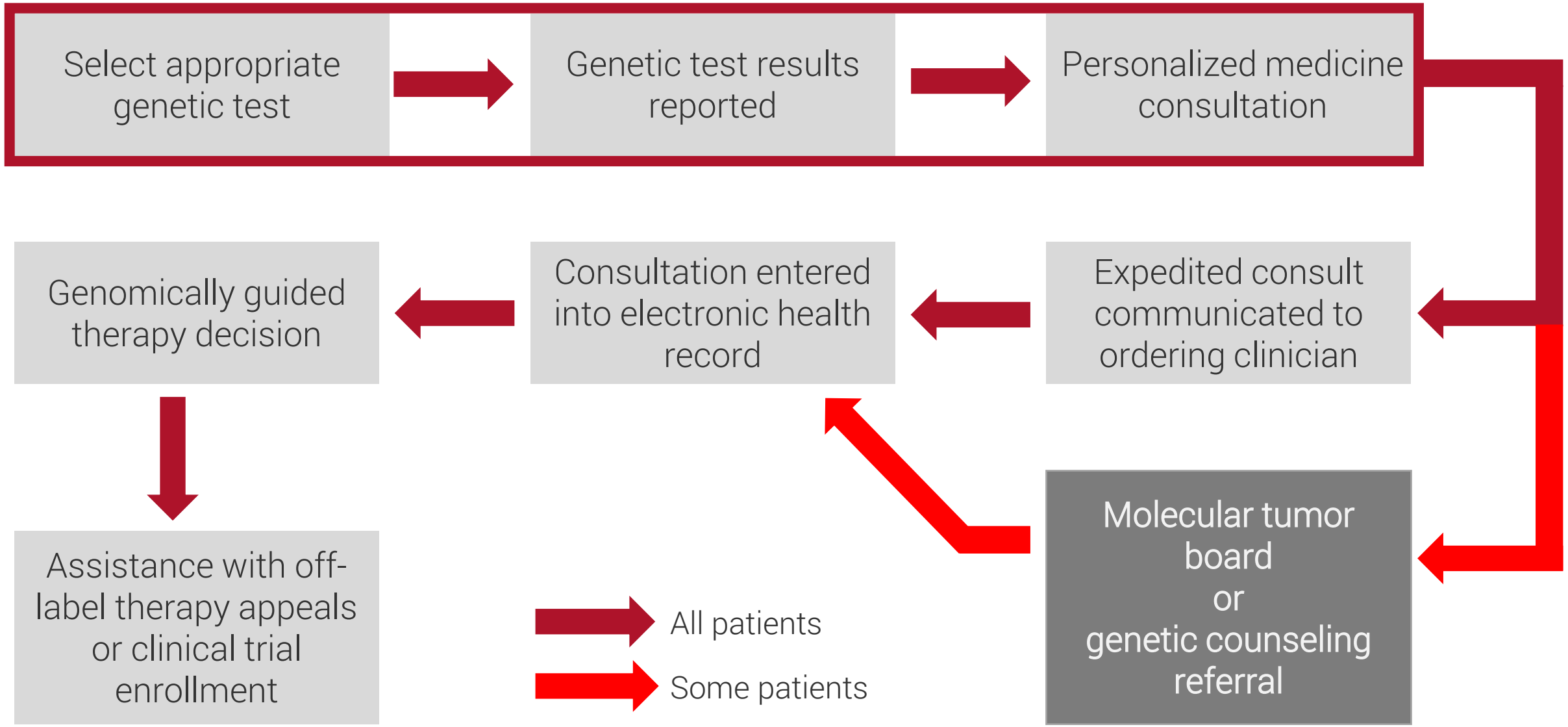
Comprehensive genomic profiling used in recent studies with large cohorts has shown that up to 90% of samples may have informative alterations.[1-6] With limited time to return results and limited amounts of tissues, a single, comprehensive assay that assesses a wide range of biomarkers increases the chances of obtaining relevant information. To help researchers address this challenge, Illumina offers TruSight library preparation, addition of unique molecular identifiers (UMIs)[7] enables detection of variants at low variant allele frequency (VAF) while simultaneously suppressing errors, thus providing high specificity. Variant-calling software is developed in concert with the assay reagents.

Table 1: Variant types detected by TruSight Oncology 500 and TruSight Oncology 500 High-Throughput

Variant type	Relevant examples
SNVs and indels	*KRAS* G12D, *EGFR* exon 19 deletions, *BRAF* V600E
Fusions	*ALK*, *ROS1*, *NTRK1*, *NTRK2*, *NTRK3*
Splice variants	*MET* exon 14
CNVs	*HER2*
MSI	MSI-High
TMB	TMB-High

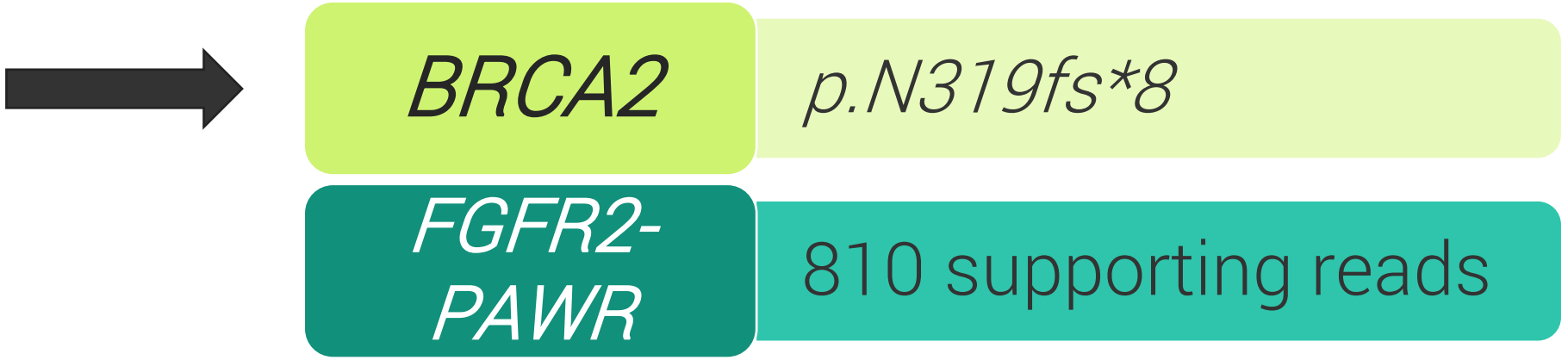
Illumina has established partnerships with several academic centers, pharmaceutical companies, and advocacy groups, to assist with the design, development, and evaluation of new oncology applications. To facilitate such endeavors, both TruSight Oncology 500 assays are easily integrated into current lab workflows (Figure 1). Using proven Illumina technology, with gene content relevant across multiple tumor types and including emerging biomarkers, TruSight Oncology 500 is well-positioned to be the foundation for developing future oncology diagnostic solutions.

Clinical Workflow



Somatic PGx Panel Findings

- Before beginning FOLFIRINOX, John's medical oncologist elected to have NGS testing performed on the liver biopsy tissue
- The chosen NGS panel covers 500+ genes in addition to RNAseq for important fusion detection
- Pertinent findings are as follows:



Somatic (or Maybe Not) Alteration in Our Clinical Scenario

- Although the chosen NGS panel is intended to sequence tumor DNA/RNA, in some cases, germline alterations may also be detected
- Mutation allele frequencies (MAFs) between 30% and 70% may have germline origin
- In high-quality tissue samples, germline variants can display MAFs of ~40%-60%
- John's NGS results reported a *BRCA2 N319fs*8* alteration with an MAF of 52%, potentially indicating a germline origin of this variant
- When a newly detected pathogenic *BRCA1/2* variant is suspected to be germline, refer to a genetic counseling service for further investigation

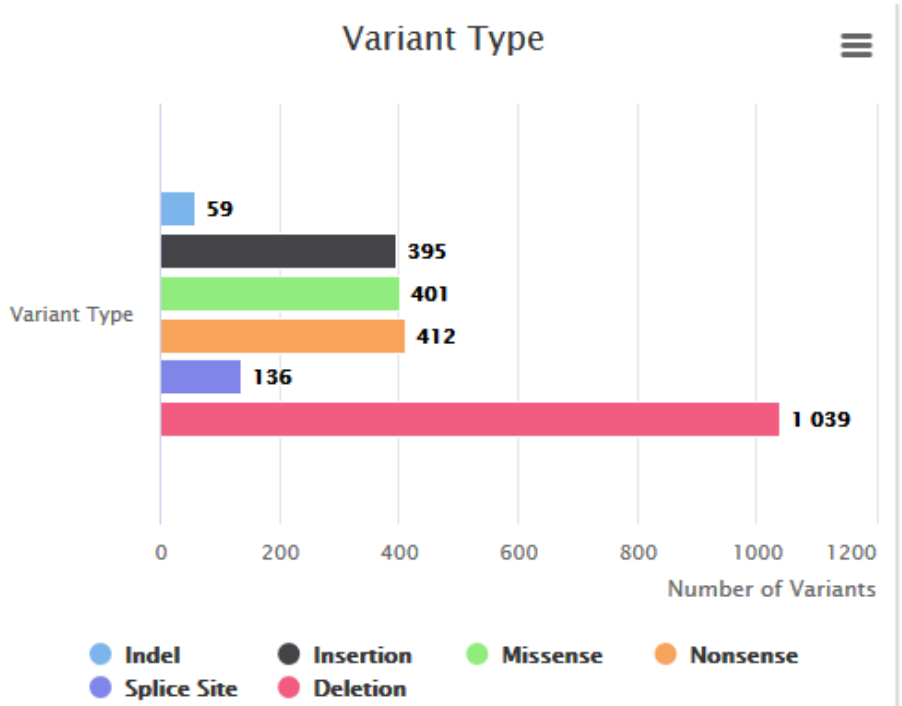
Journal of Oncology Practice 15, no. 9 (September 01, 2019) 465-473, J Natl Cancer Inst. 2016 Apr; 108(4): djv351, BMC Cancer. 2015 Apr 2;15:215

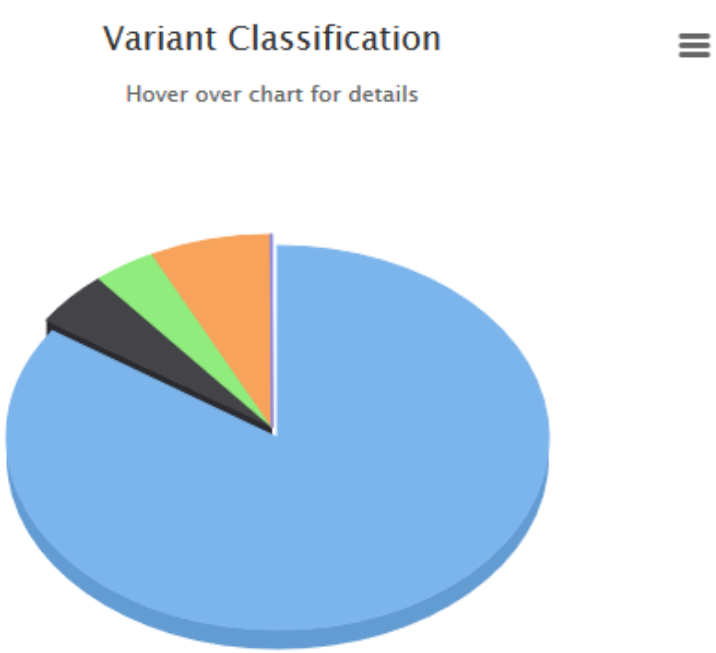
BRCA2 Database

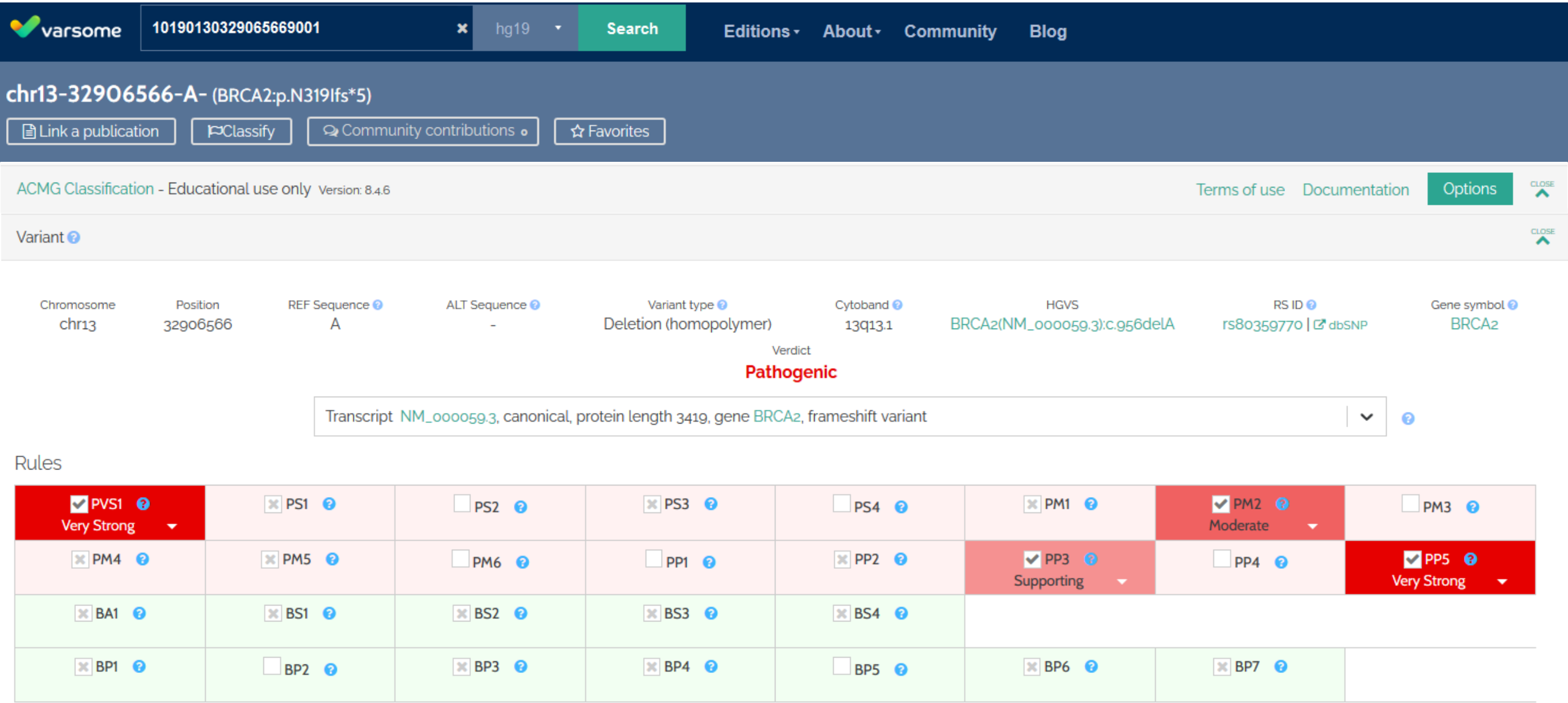
Enter *BRCA2* curated database (**2442** total entries)
Enter *BRCA2 in silico* prediction tool (covers 10,296 bases; 3,419 amino acids)

Database Information

Initial release: **January 2011**
Last update: **June 2020**



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Community contributions
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ACMG Classification - Educational use only Version: 8.4.6
Terms of use
Documentation
Options
Variant
Chromosome
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Position
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REF Sequence
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ALT Sequence
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Variant type
Deletion (homopolymer)
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HGVS
BRCA2(NM_000059.3):c.956delA
RS ID
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Gene symbol
BRCA2
Verdict
Pathogenic
Transcript NM_000059.3, canonical, protein length 3419, gene BRCA2, frameshift variant
Rules
PVS1 Very Strong
PS1
PS2
PS3
PS4
PM1
PM2 Moderate
PM3
PM4
PM5
PM6
PP1
PP2
PP3 Supporting
PP4
PP5 Very Strong
BA1
BS1
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BS3
BS4
BP1
BP2
BP3
BP4
BP5
BP6
BP7

JAMA Oncology | Original Investigation

Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome

N. Jewel Samadder, MD, MSc; Douglas Riegert-Johnson, MD; Lisa Boardman, MD; Deborah Rhodes, MD; Myra Wick, MD; Scott Okuno, MD; Katie L. Kunze, PhD; Michael Golafshar, MS; Pedro L. S. Uson Jr, MD; Luke Mountjoy, MD; Natalie Ertz-Archambault, MD; Neej Patel, MD; Eduardo A. Rodriguez, MD; Blanca Lizaola-Mayo, MD; Michael Lehrer, MD; Cameron S. Thorpe, MD; Nathan Y. Yu, MD; Edward D. Esplin, MD; Robert L. Nussbaum, MD; Richard R. Sharp, PhD; Cindy Azevedo, MS; Margaret Klint, MS; Megan Hager, MS; Sarah Macklin-Mantia, MS; Alan H. Bryce, MD; Tanios S. Bekaii-Saab, MD; Aleksandar Sekulic, MD; Keith A. Stewart, MBBS

IMPORTANCE Hereditary factors play a key role in the risk of developing several cancers. Identification of a germline predisposition can have important implications for treatment decisions, risk-reducing interventions, cancer screening, and germline testing.

OBJECTIVE To examine the prevalence of pathogenic germline variants (PGVs) in patients with cancer using a universal testing approach compared with targeted testing based on clinical guidelines and the uptake of cascade family variant testing (FVT).

Key Points

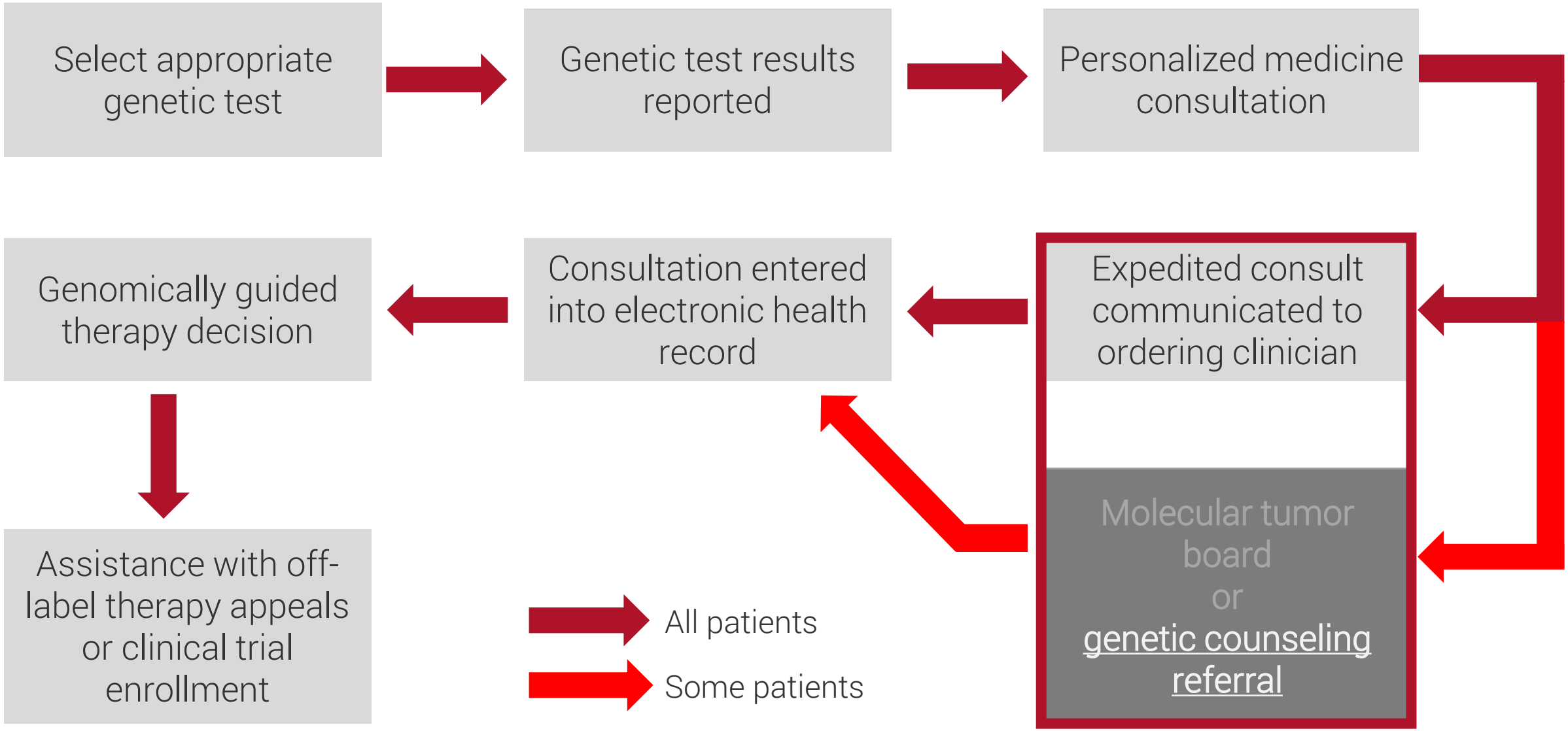
Questions Does universal genetic testing in patients with cancer identify more inherited cancer predisposition variants than a guideline-based approach, and what is the association between universal genetic testing and clinical management?

Findings In this multicenter cohort study of 2984 patients with cancer, 1 in 8 patients had a pathogenic germline variant, half of which would not have been detected using a guideline-based approach. Nearly 30% of patients with a high-penetrance variant had modifications in their treatment based on the finding.

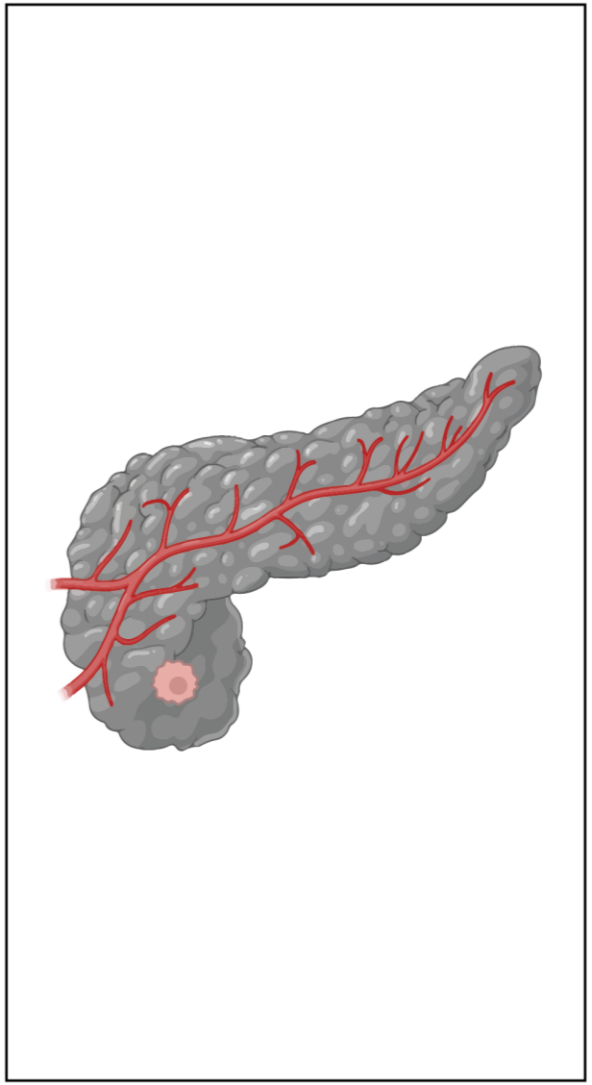
Meaning Universal genetic testing detected more clinically actionable variants than a guideline-based approach, with a significant association with clinical management for the patients and their families.

JAMA Oncol. 2020 Oct 30. doi: 10.1001/jamaoncol.2020.6252

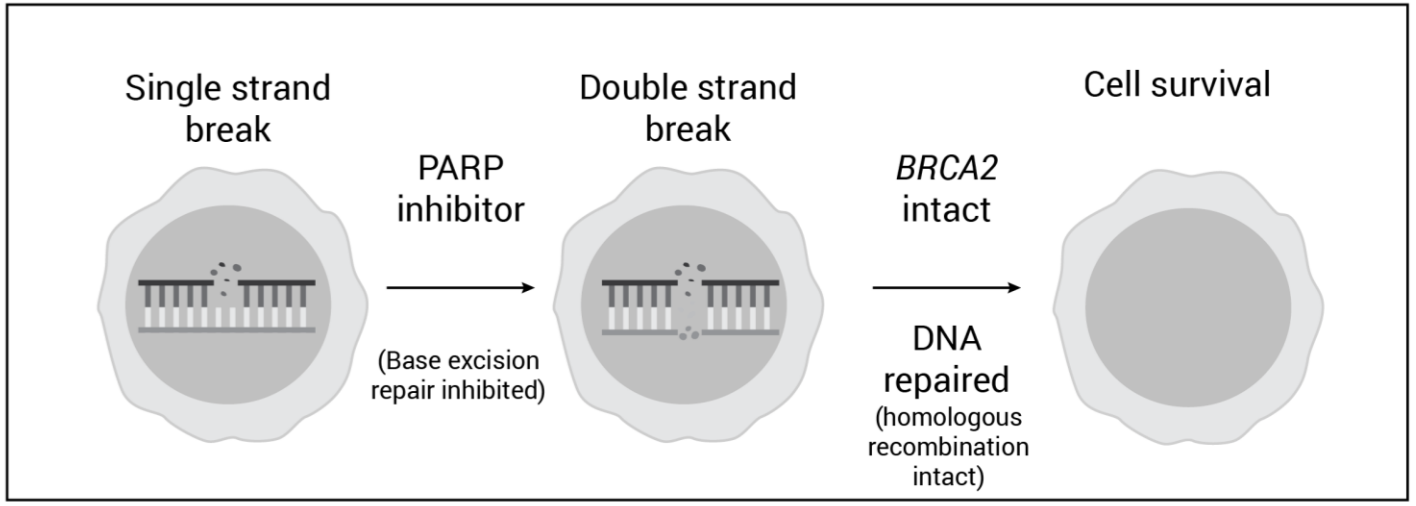
Clinical Workflow



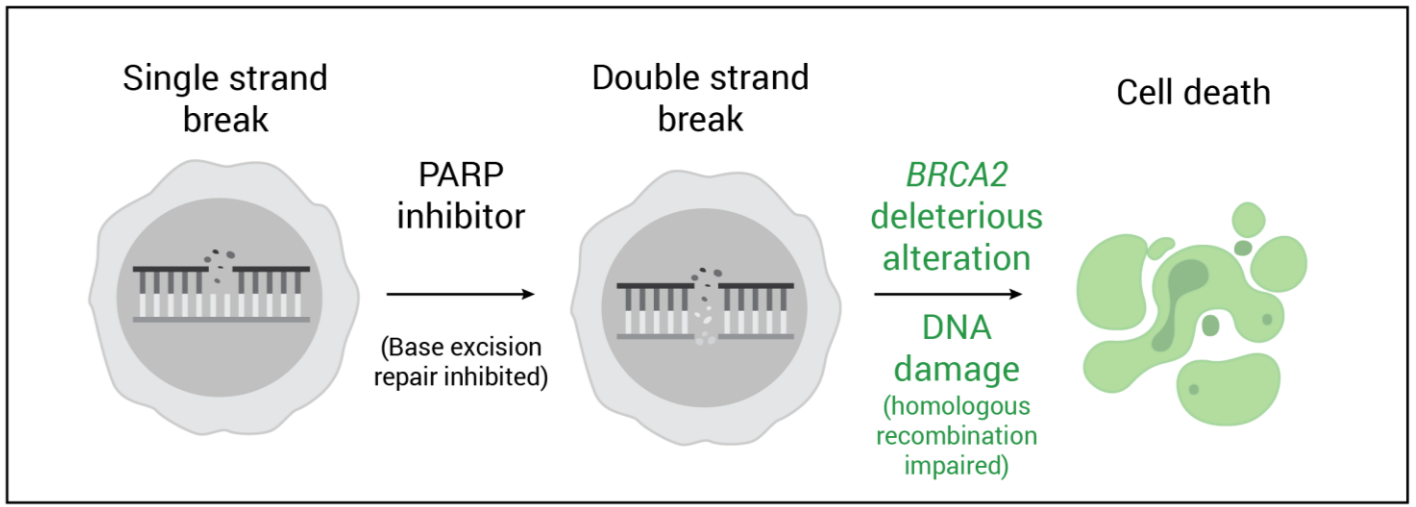
DNA Damage Response and PARP Inhibition



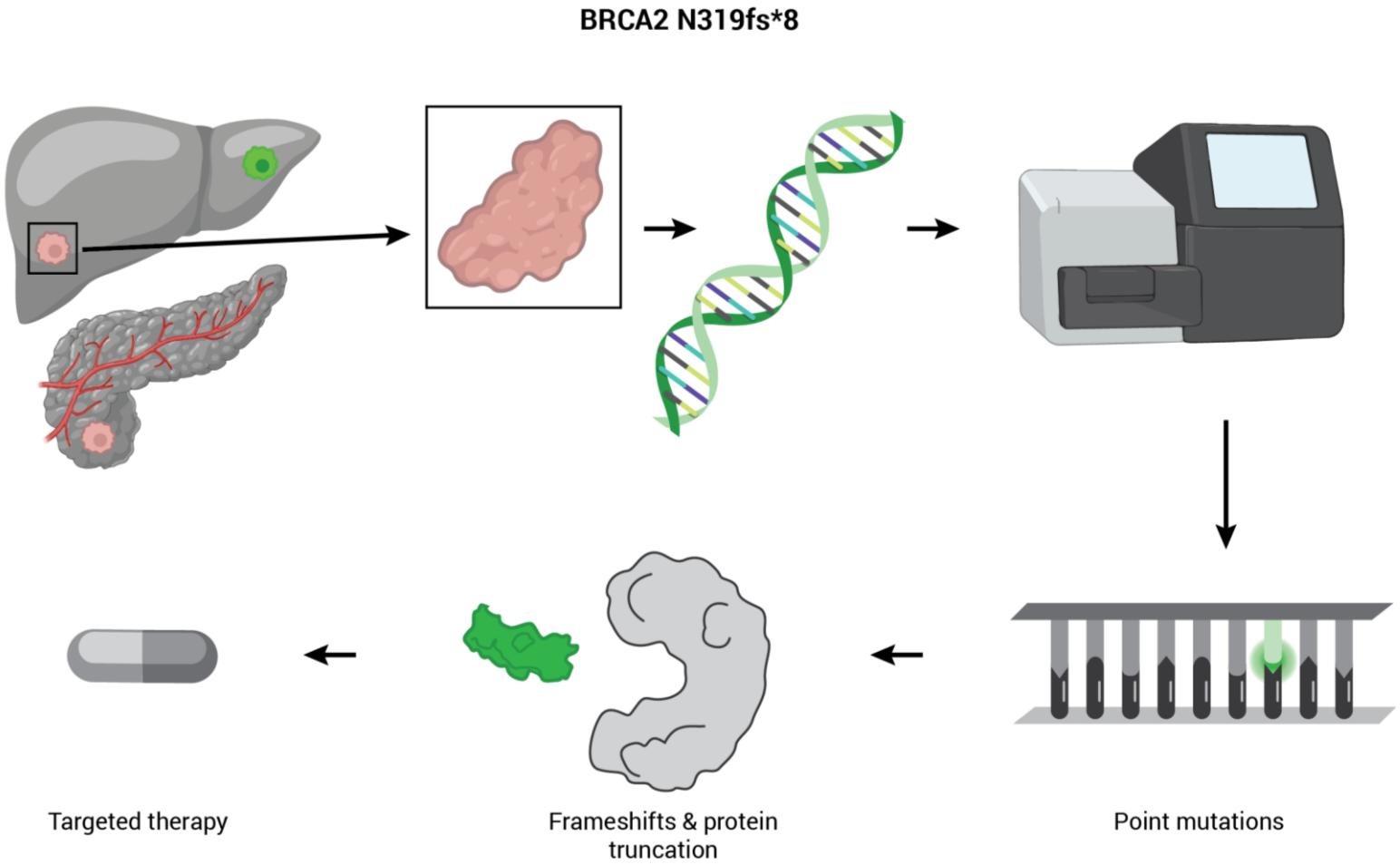
PARPi in cell with functional *BRCA2* variant



PARPi in cell with a deleterious *BRCA2* alteration



Somatic Targeted Therapies



Oxaliplatin therapy

Platin-based therapies have demonstrated clinical benefit in patients with *BRCA2* alterations.

Our patient already received oxaliplatin and received clinical benefit, supporting PARP inhibition options.
(N Engl J Med. 2019 Jul 25; 381(4):317-327)

PARP inhibition

Olaparib + cediranib clinical trial (NCT02498613)

PARP inhibitor olaparib use off-label based on recent positive findings with olaparib in patients with pancreatic cancer
(N Engl J Med. 2019 Jul 25; 381(4):317-327)

ATR inhibition

ATR inhibition has *in vitro, in vivo,* and minimal clinical data demonstrating efficacy in solid tumors (including pancreatic).

Clinical trials:
NCT02595931 (VX-970 and irinotecan)
NCT03682289 (olaparib + AZD6738)
(J Clin Oncol. 37, 2019 (suppl; abstr 3067))

POLO Trial

A phase III study investigating maintenance olaparib in patients with metastatic pancreatic cancer and **germline** *BRCA1/2* mutations who had not progressed during at least 16 weeks of first-line platinum-based chemotherapy

Outcomes	Olaparib 300 mg BID	Placebo
(n)	90	61
Median progression-free survival (PFS) (months)	7.4	3.8
Hazard ratio for disease progression/death	0.53; 95% CI, 0.35-0.82; *P* =.0038	
2-year PFS (%)	22	9.6
Overall survival	18.9	18.1
Hazard ratio for disease progression/death	0.91; 95% CI = 0.56-1.46; *P* = .68	

N Engl J Med . 2019 Jul 25;381(4):317-327

Somatic Targeted Therapies: *BRCA2* Alterations and PARP Inhibition

FDA approves olaparib for gBRCAm metastatic pancreatic adenocarcinoma

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On December 27, 2019, the Food and Drug Administration approved olaparib (LYNPARZA®, AstraZeneca Pharmaceuticals LP) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-gbrcam-metastatic-pancreatic-adenocarcinoma

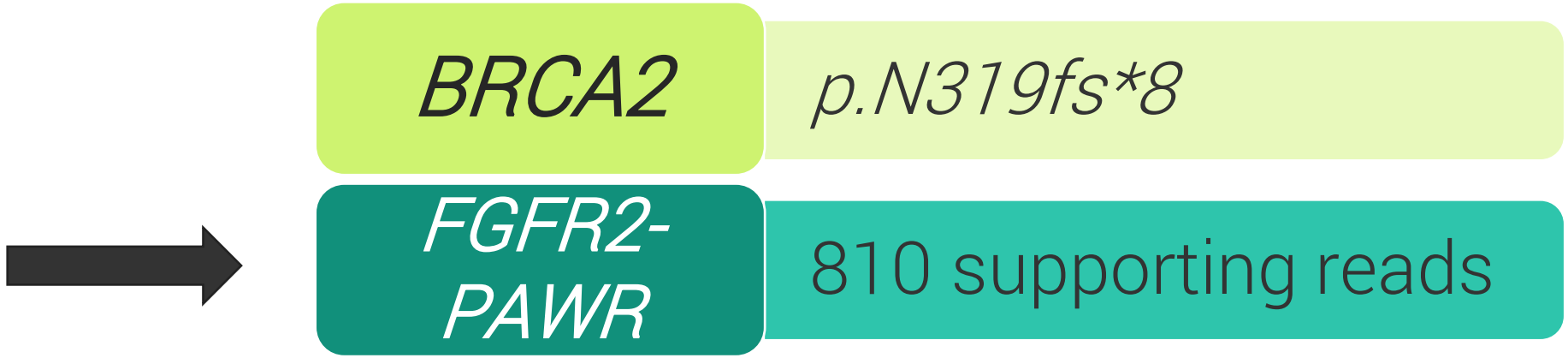
Considering Therapy Line Sequence

Although PARP inhibitor therapy may be beneficial for John based on the *BRCA2* alteration, considering the appropriate placement in his therapeutic timeline is essential.

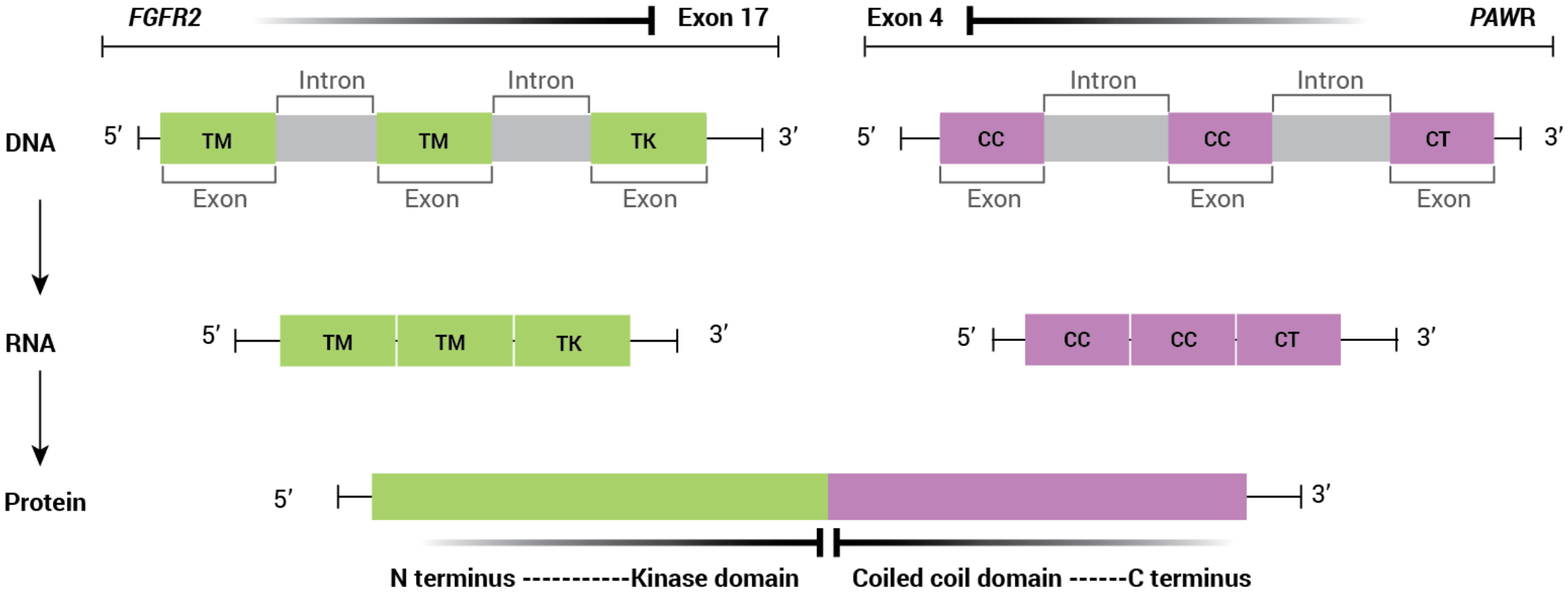
No progression on oxaliplatin (in FOLFIRINOX regimen) for at least 16 weeks is required for olaparib indication.

Somatic PGx Panel Findings

- Before beginning FOLFIRINOX, John's medical oncologist elected to have NGS testing performed on the liver biopsy tissue
- The chosen NGS panel covers 500+ genes in addition to RNA seq for important fusion detection
- Pertinent findings are as follows:

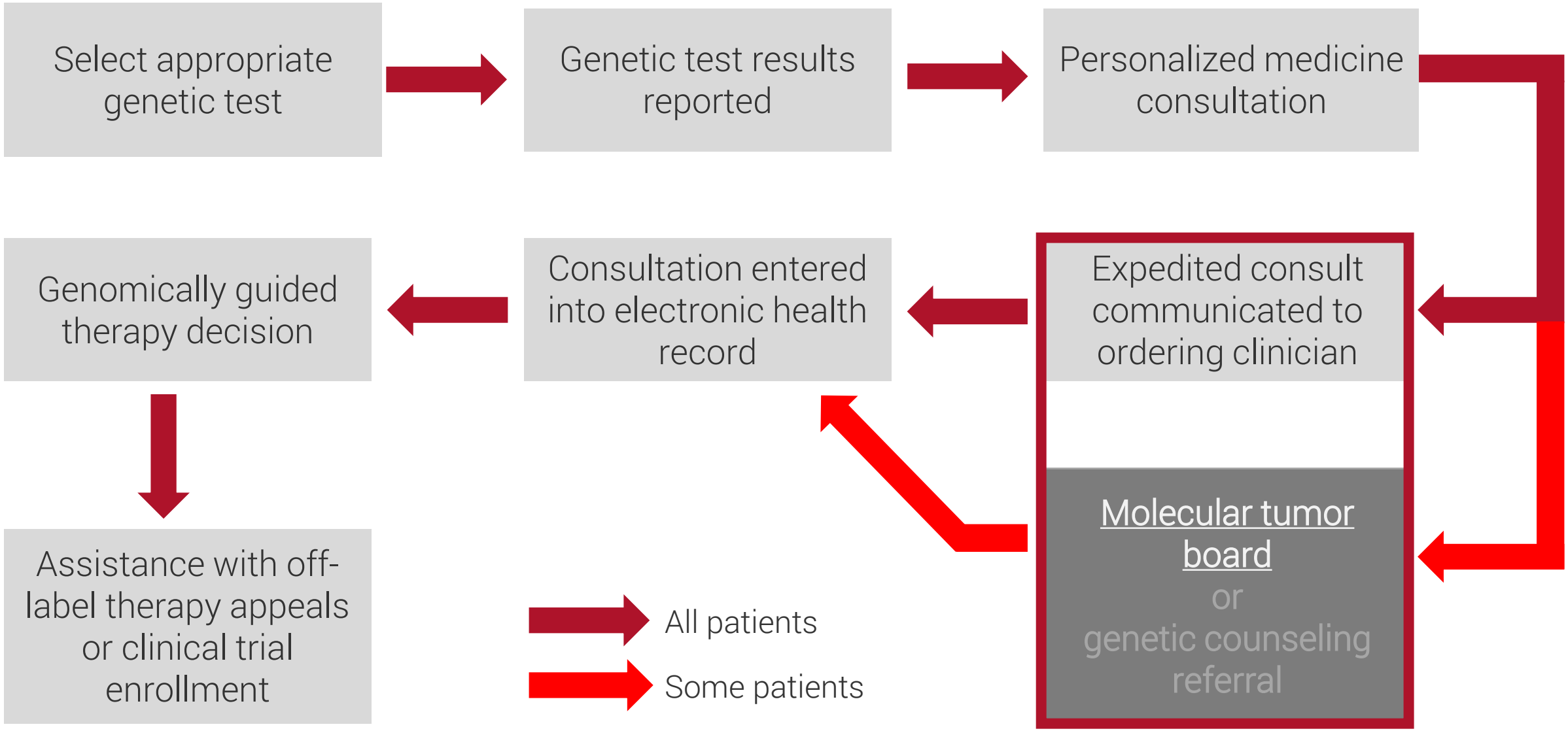


Fusion Characterization



Clin Cancer Res. 2019 May 1;25(9):2699-2707, Oncotarget. 2019 Mar 12;10(21):2095-2111.
Cancer Discov. 2013 Jun;3(6):636-47, J Pathol. 2014 Jan;232(1):4-15

Clinical Workflow



Fusion Characterization

What are the breakpoints?

- *FGFR2* exon 1 to exon 17 fused to the 5′ end of *PAWR* exon 4 to exon 7

Is the finding from DNA seq or RNA seq?

- RNA-based methods only detect functional transcripts (to avoid difficulties from intronic regions)

Are the relevant functional domains retained (eg, coiled-coil oligomerization domain)?

- Yes! The relevant functional domains are retained
- The kinase domain of *FGFR2* is retained (aa 481-757)
- *PAWR* contributes a coiled-coil domain (aa 265-334)

Actionable?

- Yes! This is an activating fusion; options include targeted therapy through off-label therapy or clinical trials
  - » Off-label treatment with erdafitinib (nonselective FGFR inhibitor)
  - » Clinical trial NCT04526106 investigating RLY-4008 (selective FGFR2 inhibitor)

Clin Cancer Res. 2019 May 1;25(9):2699-2707, Oncotarget. 2019 Mar 12;10(21):2095-2111.
Cancer Discov. 2013 Jun;3(6):636-47, J Pathol. 2014 Jan;232(1):4-15, https://clinicaltrials.gov/ct2/show/NCT04526106?term=fgfr2&recrs=a&draw=2&rank=2

Translating Recommendations into Clinical Decision-Making

- Curating and presenting available data to facilitate the decision-making process
- Considering the landscape of collective mutations
  - » Somatic *FGFR2* fusion + germline *BRCA2* mutation
- Consideration of each patient's unique characteristics
  - » John's preference about treatment options
  - » Where John is in his treatment course (sequencing of treatment options)
  - » Availability and ability to qualify for a clinical trial
  - » Insurance coverage and ability to afford off-label therapy

Summary of Therapy Recommendations

- 50% reduction in dose of 5-FU (*DPYD* IM)
- Consider alternative therapies for ondansetron, tramadol, and paroxetine (*CYP2D6* UM) (perhaps granisetron, morphine, citalopram)
- After confirmation from genetic counseling that the *BRCA2* frameshift mutation is pathogenic and germline, and after at least 16 weeks without progression on FOLFIRINOX, maintenance olaparib therapy can be considered
- For a later line therapy option, off-label treatment with erdafitinib or a clinical trial investigating RLY-4008 can be considered

Somatic PGx Summary Points

- Selecting an appropriate test for your patient is essential
- Not all reported mutations on a somatic panel are guaranteed to be somatic.
  - » Coordinating with genetic counseling is essential
- Solid tumor panels are great at detecting the alterations of an individual tumor
- ctDNA panels are helpful for detecting recurrence, clonal expansion, and collective genomic landscape of heterogeneous tumors

Tying It All Together

- Germline and somatic PGx can both be used throughout an individual patient's course of cancer care
- Reported findings from PGx panels can lead to opportunities to optimize treatment and reduce the risk of harm
- PGx panels offer us a lens into therapeutic indicators that we are otherwise not detecting
- Not all PGx tests are the same; knowing what you are looking for and verifying what the panel can find is essential

ARUP® LABORATORIES

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