Genomic Standards and Knowledge Bases for Decision Support

Jeremy Warner M.D., M.S.
Associate Professor of Medicine and Biomedical Informatics
Vanderbilt University
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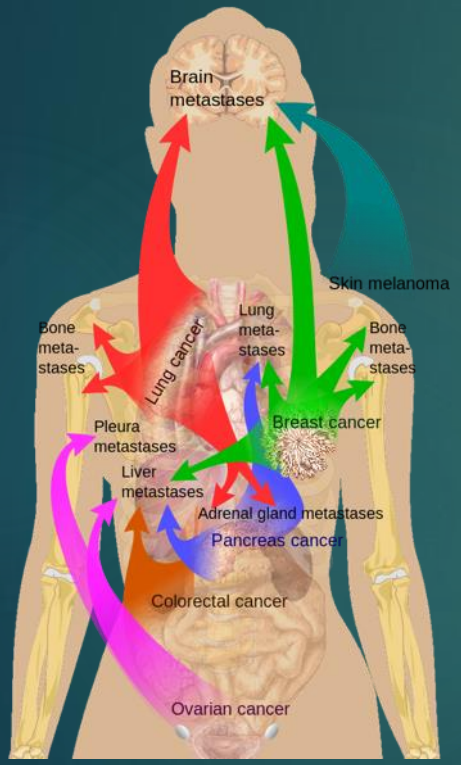
Disclosures

NIH funding: P30 CA068485, R01 HL133786, R01 LM010685, U24 CA184407, U24 CA194215, U2C OD023196

Ownership: co-founder, HemOnc.org LLC

Three questions that every cancer patient asked (c. 3000 BCE – May 2001)



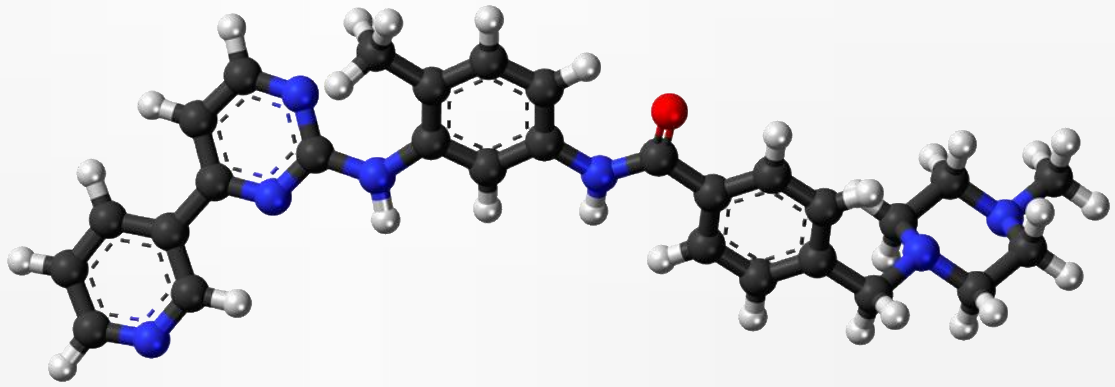
Source: Wikipedia

- Who's like me? **Diagnosis**
- How long have I got? **Prognosis**
- What are my options? **Prediction**

Drug Approval Package

Gleevec (Imatinib Mesylate) Capsules
Company: Novartis Pharmaceuticals Corporation
Application No.: 21-335
Approval Date: 5/10/2001

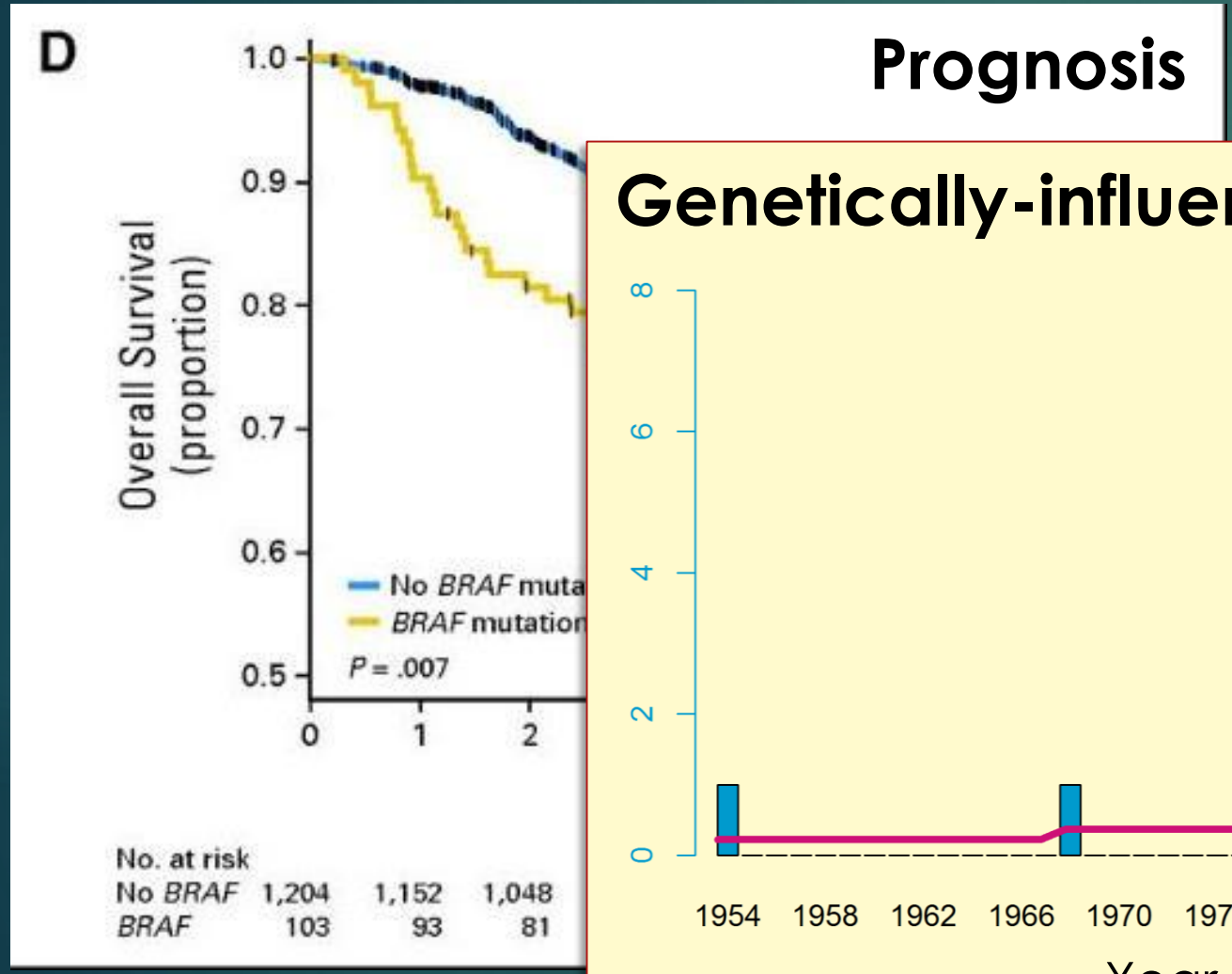
- Approval Letter(s) (PDF)
- Printed Labeling (PDF)
- Medical Review(s)
  Part 1 (PDF)
  Part 2 (PDF)
  Part 3 (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s)
  Part 1 (PDF)
  Part 2 (PDF)
- Statistical Review(s) (PDF)
- Clinical Pharmacology Biopharmaceutics Review(s)



Source: Wikipedia

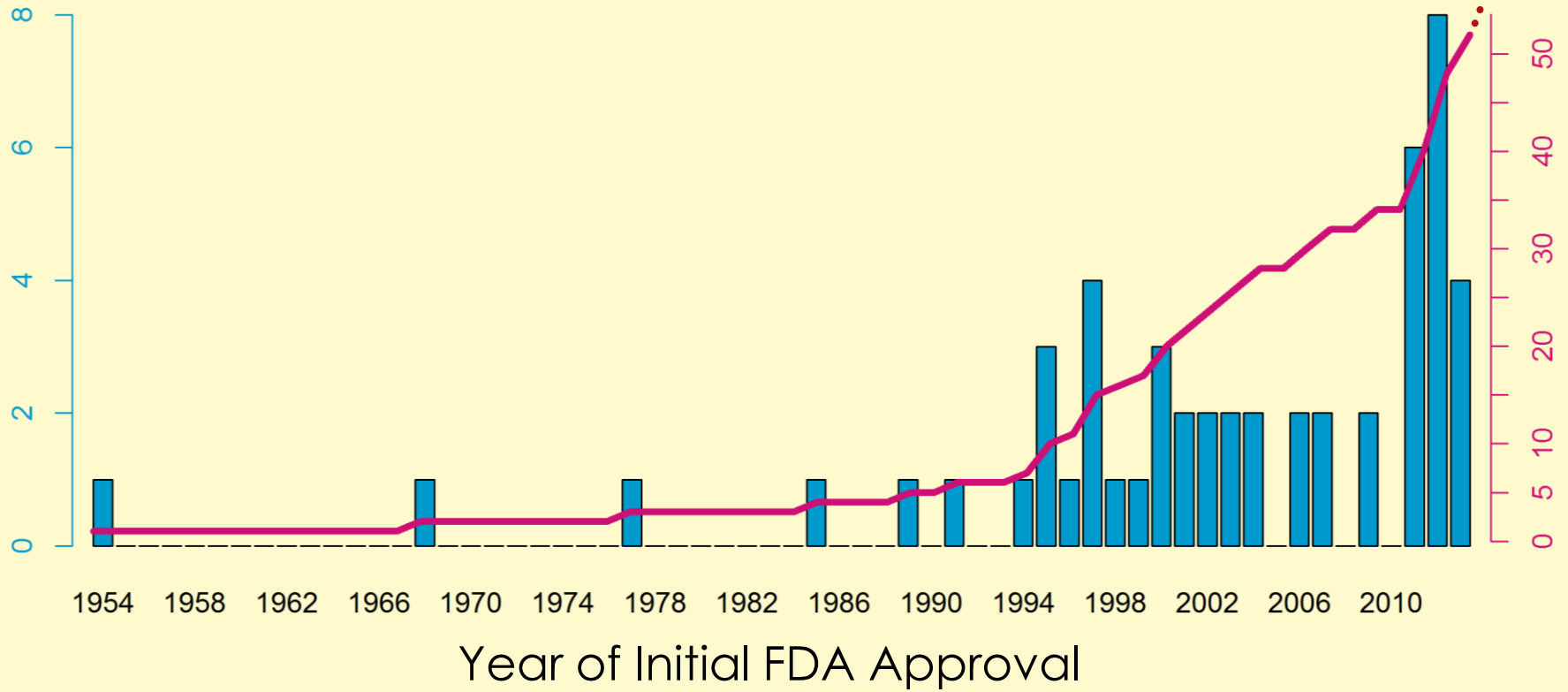
Biomarkers

Prognosis



Arnaud D. Roth et al. JCO 2010;28:466-474

Genetically-influenced cancer treatments



Three questions that every *genomically-informed* cancer patient asks (c. 2001-)

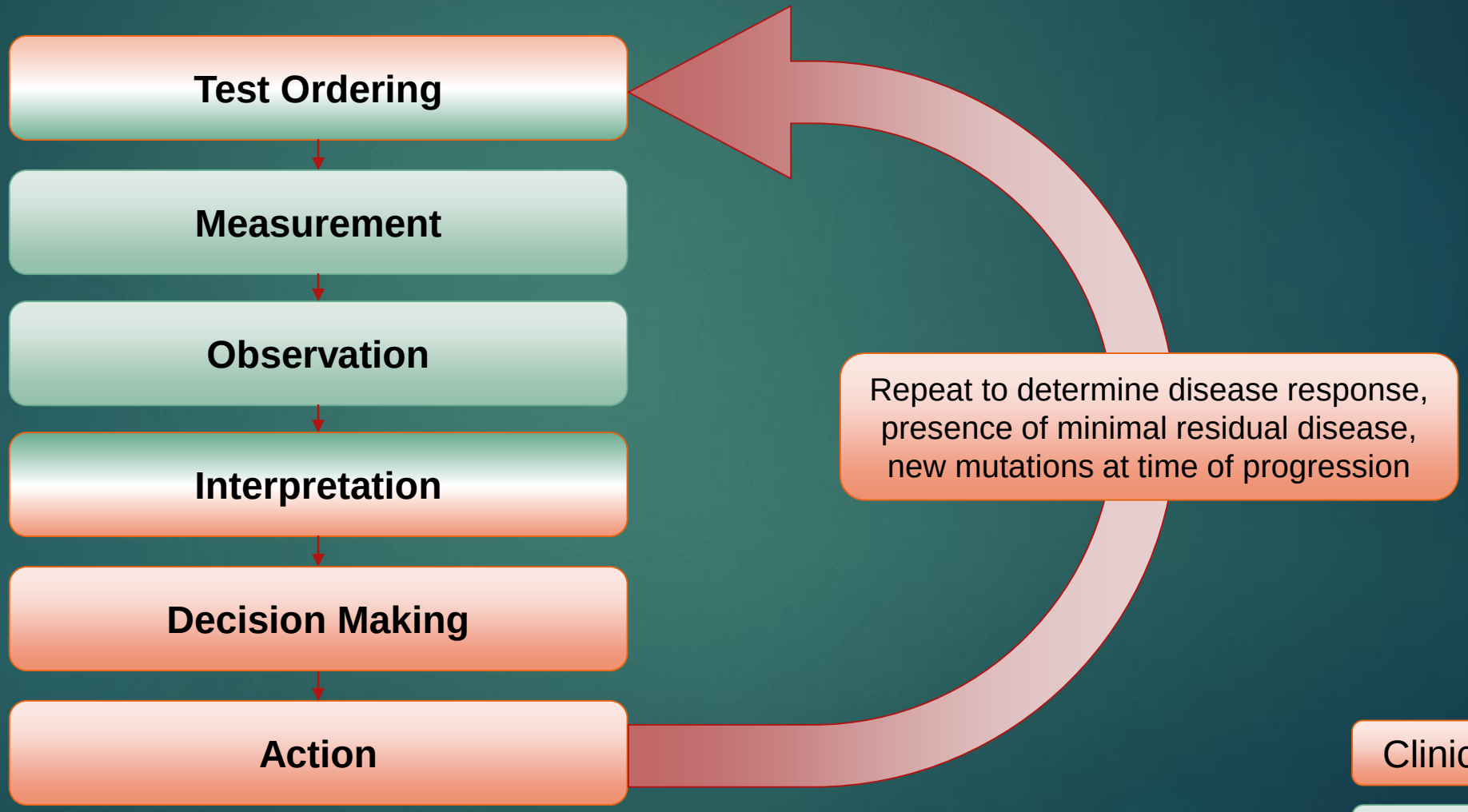
- ~~Who's like me?~~
- ~~How long have I got?~~
- What are my options?

Precision oncology: a definition

- Right patient
- Right treatment
- Right time

- In 2018, the potential to achieve these goals appears to be primarily through cancer molecular profiling, targeted agents, (and immunotherapy)

Precision oncology decision making



Warner et al. doi: 10.1186/s13073-016-0371-3

2001-2010: Ad hoc genomic testing

EGFR

2004: EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib[1]

KRAS

2006: *KRAS* mutation status is predictive of response to cetuximab therapy in colorectal cancer[2]

BRAF

2010: Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma[3]

1. Pao et al. doi:10.1073/pnas.0405220101
2. Lièvre et al. doi: 10.1158/0008-5472.CAN-06-0191
3. Bollag et al. doi: 10.1038/nature09454

2011: SNaPshot Panels:

"Driver" Genes Providing "Actionable" Results

Lung cancer:

EGFR, KRAS, PIK3CA, BRAF, NRAS, MEK, AKT1, PTEN

Melanoma:

NRAS, BRAF, KIT, CTNNB1, GNAQ, GNA11

Colon cancer:

KRAS, BRAF, AKT1, PIK3CA, SMAD4, PTEN, NRAS

Breast cancer:

PIK3CA, PTEN, AKT1

Glioma:

IDH1, IDH2, BRAF

Acute Myeloid Leukemia:

IDH1, IDH2, FLT3-TKD, DNMT3A, KIT

Table 1. List of PCR Primers for the SNaPshot Screen

Name	Sequence
AKT1_ex2_a1	5′-GAGGGTCTGACGGGTAGAGT-3′
AKT1_ex2_a2	5′-TCTTGAGGAGGAAGTAGCGT-3′
BRAF_ex11_a1*	5′-TCTGTTTGGCTTGACTTGACTT-3′
BRAF_ex11_a2*	5′-TCACCACATTACATACTTACCATGC-3′
BRAF_ex15_a1*	5′-TGCTTGCTCTGATAGGAAAATG-3′
BRAF_ex15_a2*	5′-CTGATGGGACCCACTCCAT-3′
EGFR_ex18_a1*	5′-CCAACCAAGCTCTCTTGAGG-3′
EGFR_ex18_a2*	5′-CCTTATACACCGTGCCGAAC-3′
EGFR_ex20_a1*	5′-TGTTCCCGGACATAGTCCAG-3′
EGFR_ex20_a2*	5′-ATCTGCCTCACCTCCACCGT-3′
EGFR_ex21_a1*	5′-CCTCCTTCTGCATGGTATTC-3′
EGFR_ex21_a2*	5′-GCAGCATGTCAAGATCACAG-3′
KRAS_ex2_a1*	5′-TCATTATTTTTATTATAAGGCCTGCTG-3′
KRAS_ex2_a2*	5′-AGAATGGTCCTGCACCAGTAA-3′
KRAS_ex3_a1*	5′-AATTGATGGAGAAACCTGTCTCTTG-3′
KRAS_ex3_a2*	5′-TGGTCCCTCATTGCACTGTA-3′
MEK1_ex2_a1	5′-AGCGAAAGCGCCTTGAGGCCTT-3′
MEK1_ex2_a2	5′-AACACCACACCGCCATTGCCAG-3′
NRAS_ex3_a1	5′-ATAGATGGTGAAACCTGTTTGTTGG-3′
NRAS_ex3_a2	5′-TGTATTGGTCTCTCATGGCACT-3′
PIK3CA_ex9_a1*	5′-GACAAAGAACAGCTCAAAGCAA-3′
PIK3CA_ex9_a2*	5′-TTTAGCACTTACCTGTGACTCCA-3′
PIK3CA_ex20_a1*	5′-GAGCAAGAGGCTTTGGAGTA-3′
PIK3CA_ex20_a2*	5′-ATCCAATCCATTTTTGTTGTCC-3′
PTEN_ex7_a1*	5′-GGTGAAGATATATTCCTCCAATTCA-3′
PTEN_ex7_a2*	5′-TTCTCCCAATGAAAGTAAAGTACAAA-3′

*Published previously.[12]

Su et al. doi: 10.1016/j.jmoldx.2010.11.010.

2014: Complexity increases

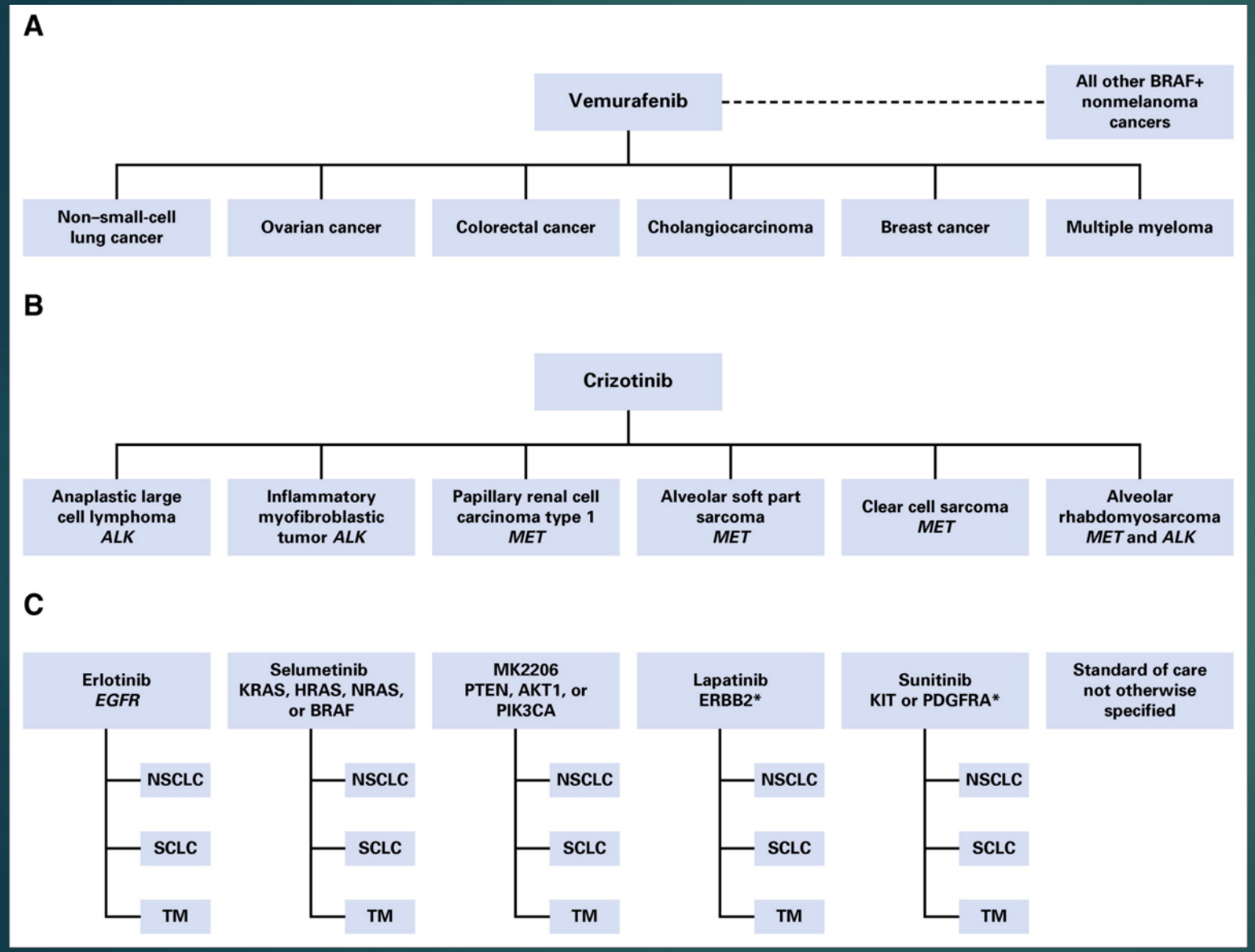
Foundation One® CURRENT GENE LIST

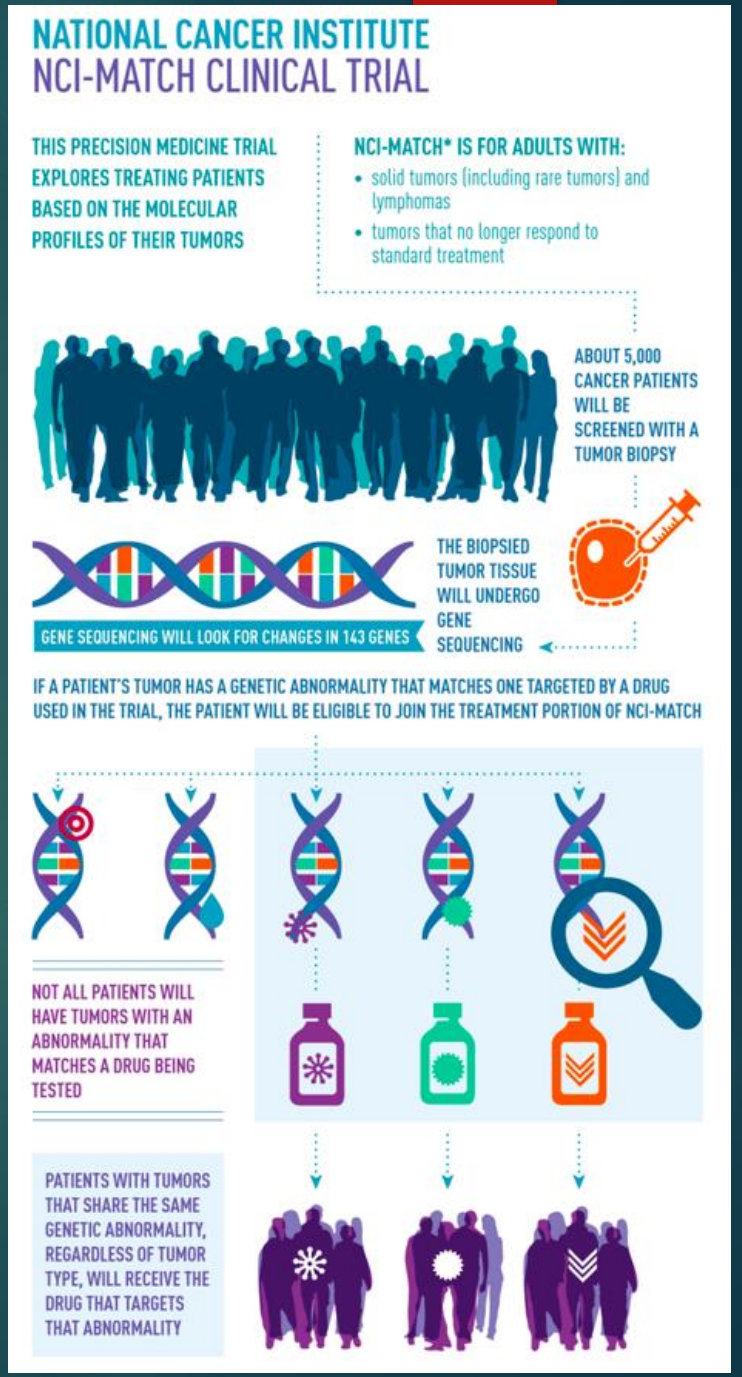
ABL1	C11orf30 (EMSY)	DDR2	FGFR4	IL7R	MET	PIK3CA	SDHD	TSHR
ABL2	CARD11	DICER1	FH	INHBA	MITF	PIK3CB	SETD2	U2AF1
ACVR1B	CBFB	DNMT3A	FLCN	INPP4B	MLH1	PIK3CG	SF3B1	VEGFA
AKT1	CBL	AURKA	CDKN2A	FANCC	GNA13	KMT2A (MLL)	NOTCH2	QKI	STAG2
AKT2	CCND1	AURKB	CDKN2B	FANCD2	GNAQ	KMT2C (MLL3)	NOTCH3	RAC1	STAT3
AKT3	CCND2	AXIN1	CDKN2C	FANCE	GNAS	KMT2D (MLL2)	NPM1	RAD50	STAT4
ALK	CCND3	AXL	CEBPA	FANCF	GPR124	KRAS	NRAS	RAD51	STK11
AMER1 (FAM123B)	CCNE1	BAP1	CHD2	FANCG	GRIN2A	LMO1	NSD1	RAF1	SUFU
APC	CD274	BARD1	CHD4	FANCL	GRM3	LRP1B	NTRK1	RANBP2	SYK
AR	CD79A	BCL2	CHEK1	FAS	GSK3B	LYN	NTRK2	RARA	TAF1
ARAF	CD79B	BCL2L1	CHEK2	FAT1	H3F3A	LZTR1	NTRK3	RB1	TBX3
ARFRP1	CDC73	BCL2L2	CIC	FBXW7	HGF	MAGI2	NUP93	RBM10	TERC
ARID1A	CDH1	BCOR	CREBBP	FGF10	HNF1A	MAP2K1	PAK3	RET	TERT (promoter only)
ARID1B	CDK12	BCORL1	CRKL	FGF14	HRAS	MAP2K2	PALB2	RICTOR	TET2
ARID2	CDK4	BLM	CRLF2	FGF19	HSD3B1	MAP2K4	PARK2	RNF43	TGFBR2
ASXL1	CDK6	BRAF	CSF1R	FGF23	HSP90AA1	MAP3K1	PAX5	ROS1	TNFAIP3
ATM	CDK8	BRCA1	CTCF	FGF3	IDH1	MCL1	PBRM1	RPTOR	TNFRSF14
ATR	CDKN1A	BRCA2	CTN						
ATRX	CDKN1B	BRD4	CTN						
		BRIP1	CU						
		BTG1	CY						
		BTK	DA						

SELECT REARRANGEMENTS

ALK	BRAF	BRD4	ETV4	ETV6	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	

Molecular basket trials





Cunanan et al. doi: 10.1200/JCO.2016.69.9751

ASCO TAPUR™

Targeted Agent and Profiling Utilization Registry Study

Enrollment by Drug as of 2/1/18

Drug Name	Total participants enrolled on drug
Axitinib (INLYTA)	4
Bosutinib (BOSULIF)	1
Cetuximab (ERBITUX)	54
Cobimetinib (COTELLIC) + Vemurafenib (ZELBORAF)	34
Crizotinib (XALKORI)	15
Dasatinib (SPRYCEL)	8
Erlotinib (TARCEVA)	1
Nivolumab (OPDIVO) + Ipilimumab (YERVOY)	13
Olaparib (LYNPARZA)	87
Palbociclib (IBRANCE)	134
Pembrolizumab (KEYTRUDA)	68
Pertuzumab (PERJETA) + Trastuzumab (HERCEPTIN)	47
Regorafenib (STIVARGA)	15
Sunitinib (SUTENT)	87
Temsirolimus (TORISEL)	55
Vismodegib (ERIVEDGE)	5
Total	628

113 Sites, 20 states

7 Pharma partners

- AstraZeneca (1)
- Bayer (1)
- Bristol-Meyers Squibb (3)
- Eli Lilly (1)
- Genentech (6)
- Merck (1)
- Pfizer (6)

ASCO

Slide courtesy of Richard Schilsky MD, FACP, FSCT, FASCO

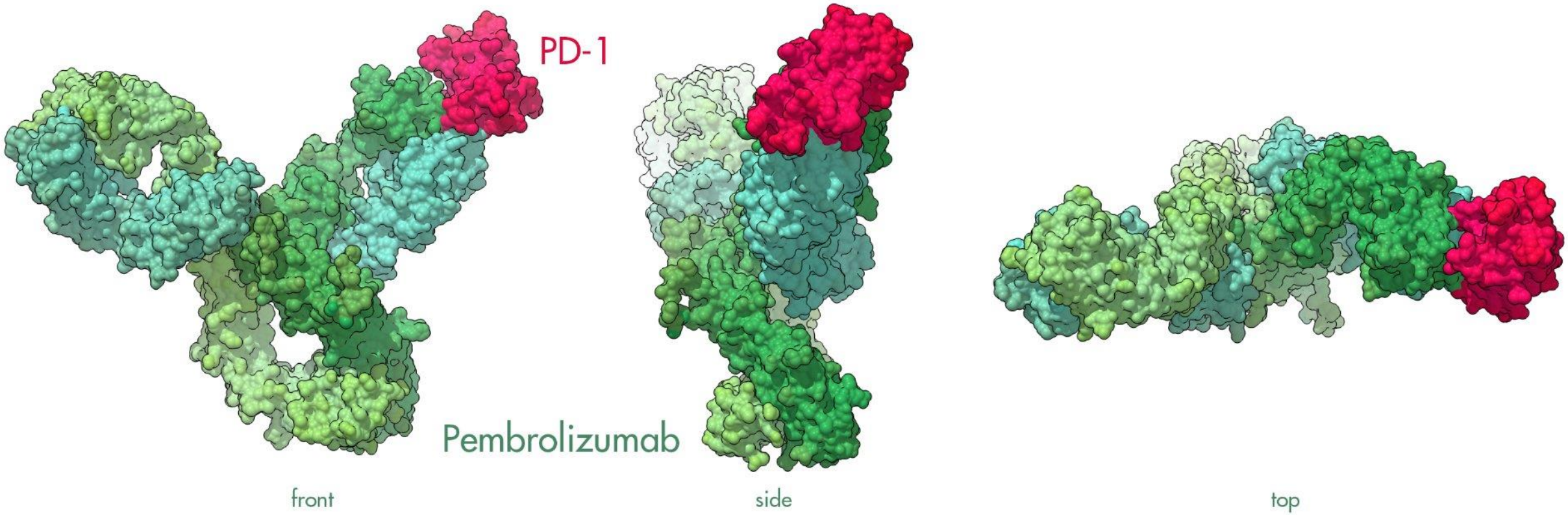
Precision Oncology and the FDA:
Scope of approvals is changing

Year of Approval*	Traditional	Targeted**	Gene mutation-specific	FDA gene mutation-specific requirement
2010	2	2		
2011	1	4	3	**2 (25%)**
2012	2	8	2	
2013	1	4	3	**4 (50%)**
2014		8	1	**5 (56%)**
2015	3	10	3	**4 (25%)**
2016		4		**3 (75%)**
2017	1	15	3	**3 (100%)**

*New hematology/oncology approvals only, not including biosimilars
**Including immunotherapy and CAR-T cell therapy

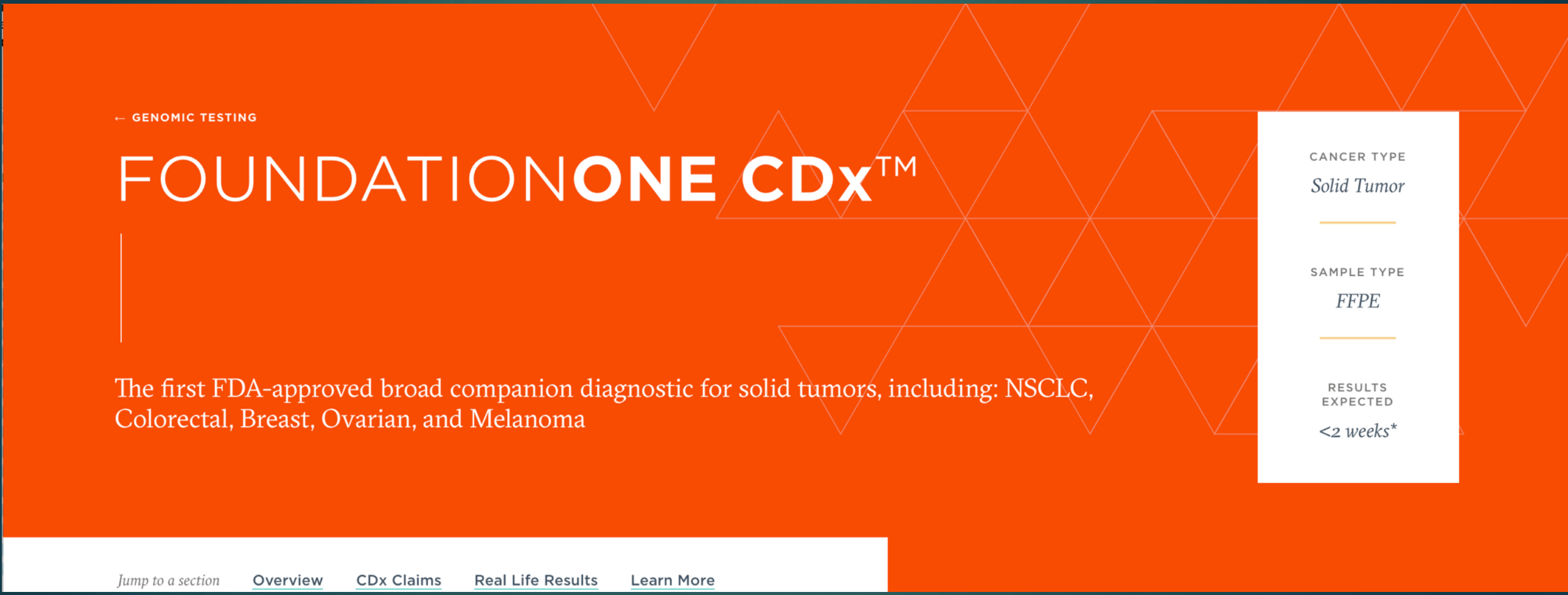
Game changer #1: May 2017

Pembrolizumab: now FDA approved for any solid tumor with MSI-H or dMMR status



https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm

Game changer #2: Nov 2017



https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587273.htm

Cancer Molecular Profile Report Examples

PATIENT RESULTS

4 genomic alterations

4 therapies associated with potential clinical benefit

0 therapies associated with lack of response

7 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified†

STK11 Q170*
CDKN2A loss
TP53 W91*
KDM6A truncation exon 11

Additional Disease-relevant Genes with No Reportable Alterations Detected

ALK
KRAS
EGFR

†For a complete list of the genes assayed, please refer to the Appendix
⌘See Appendix for details

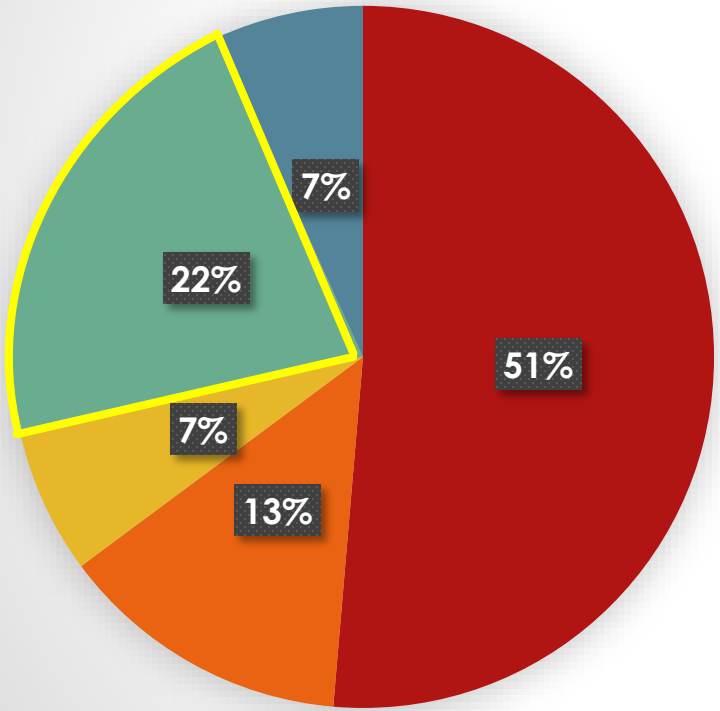
THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
STK11 Q170*	None	Bosutinib Dasatinib Everolimus Temsirolimus	Yes, see clinical trials section
CDKN2A loss	None	None	Yes, see clinical trials section
TP53 W91*	None	None	Yes, see clinical trials section
KDM6A truncation exon 11	None	None	None

Credit: Dr. Subha Madhavan and the Georgetown Lombardi Cancer Center

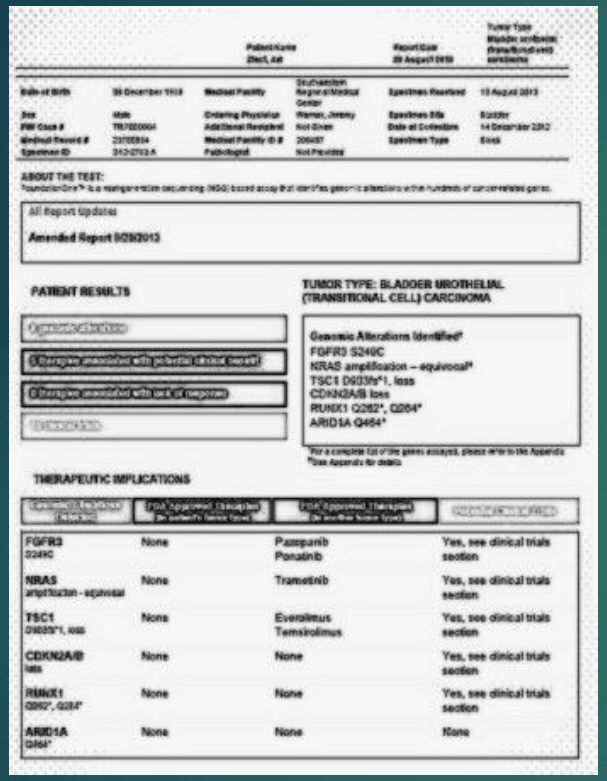
Moving the data

When you order a somatic cancer gene panel (a.k.a. cancer molecular profile), does your lab send (this could be an in-house or external lab) and can your EHR store discrete data results?



Poll of ASCO membership, 2016

Cancer molecular profile reporting



Patient Name
Report Date
Tumor Type

Date of Birth | Medical Facility | Specimen Received
Sex | Ordering Physician | Specimen Site
FMI Case # | Additional Recipient | Date of Collection
Medical Record # | Medical Facility ID # | Specimen Type
Specimen ID | Pathologist

ABOUT THE TEST:

All Report Updates

Amended Report 8/29/2013

PATIENT RESULTS

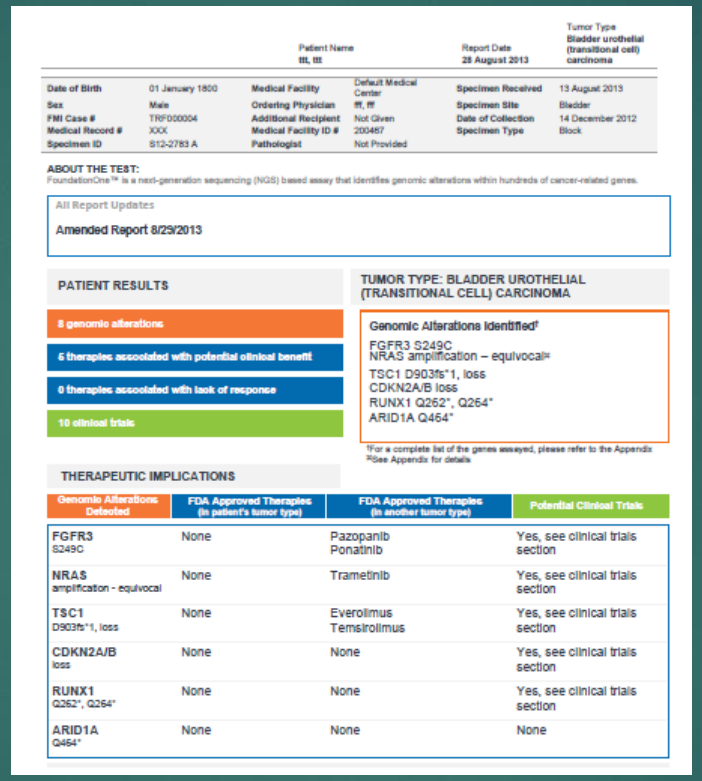
TUMOR TYPE: BLADDER UROTHELIAL (TRANSITIONAL CELL) CARCINOMA

Genomic Alterations Identified*
FGFR3 S249C
NRAS amplification – equivocal*
TSC1 D903fs*1, loss
CDKN2A/B loss
RUNX1 Q262*, Q264*
ARID1A Q464*

*For a complete list of the genes assayed, please refer to the Appendix
*See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
FGFR3 S249C	None	Pazopanib Ponatinib	Yes, see clinical trials section
NRAS amplification - equivocal	None	Trametinib	Yes, see clinical trials section
TSC1 D903fs*1, loss	None	Everolimus Temsirolimus	Yes, see clinical trials section
CDKN2A/B loss	None	None	Yes, see clinical trials section
RUNX1 Q262*, Q264*	None	None	Yes, see clinical trials section
ARID1A Q464*	None	None	None



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ABOUT THE TEST:

All Report Updates

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PATIENT RESULTS

8 genomic alterations
6 therapies associated with potential clinical benefit
0 therapies associated with lack of response
10 clinical trials

TUMOR TYPE: BLADDER UROTHELIAL (TRANSITIONAL CELL) CARCINOMA

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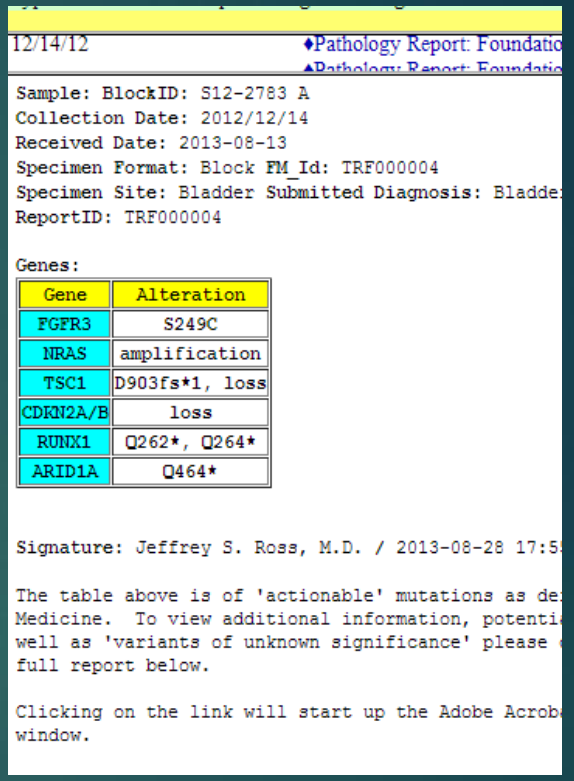
RUNX1 Q262*, Q264*	None	None	Yes, see clinical trials section
ARID1A Q464*	None	None	None



12/14/12 ♦Pathology Report: Foundatio

Sample: BlockID: S12-2783 A
Collection Date: 2012/12/14
Received Date: 2013-08-13
Specimen Format: Block FM_Id: TRF000004
Specimen Site: Bladder Submitted Diagnosis: Bladde
ReportID: TRF000004

Genes:

Gene	Alteration
FGFR3	S249C
NRAS	amplification
TSC1	D903fs*1, loss
CDKN2A/B	loss
RUNX1	Q262*, Q264*
ARID1A	Q464*

Signature: Jeffrey S. Ross, M.D. / 2013-08-28 17:5

The table above is of 'actionable' mutations as de
Medicine. To view additional information, potenti
well as 'variants of unknown significance' please
full report below.

Clicking on the link will start up the Adobe Acrob
window.

Better! (but still custom)

Rioth et al. doi: 10.1200/JOP.2015.008276

SMART on FHIR Genomics: facilitating standardized clinico-genomic apps

RECEIVED 20 December 2014
REVISED 10 April 2015
ACCEPTED 18 April 2015
PUBLISHED ONLINE FIRST 21 July 2015

Gil Alterovitz[1,2,3,*], Jeremy Warner[4,5,*], Peijin Zhang[6,*], Yishen Chen[7], Mollie Ullman-Cullere[8], David Kreda[2], Isaac S. Kohane[1,2,3]

AMIA [INFORMAT]CS PROFESS[ONALS. LEAD]NG THE WAY.
OXFORD UNIVERSITY PRESS

c. GeneticObservation			
AssessedCondition[1]	Condition	1	Condition described by this observation
SourceSeq[2]	Sequence	0..*	Sequence resource linked to this observation
DNASequenceVariation[4]	String	0..*	HGVS nomenclature for cDNA variant
GeneId[4]	CodeableConcept	0..*	HGNC identifier and symbol
VariantTranscript ReferenceSequenceId[4]	CodeableConcept	0..*	cDNA reference sequence identifier either RefSeq or ENSEMBL
DNASequenceVariationType[4]	CodeableConcept	0..*	Classification of variant change using LOINC Answer List values 48019-4 or Sequence Ontology values
DNARegionName[4]	String	0..*	Gene region containing the variant, eg, Exon 19
ProteinReference SequenceId[4]	CodableConcept	0..*	Protein reference sequence identifier either RefSeq or ENSEMBL
AminoAcidChange[4]	String	0..*	HGVS nomenclature for amino acid change
AminoAcidChangeType[4]	CodableConcept	0..*	Classification of variant change using LOINC Answer List values 48019-4 or Sequence Ontology values
VariationId[4]	CodableConcept	0..*	Variant identifier in ClinVar, dbSNP, or COSMIC
AlleleName[4]	String	0..*	Common name for variant for display purposes
AllelicState[4]	CodableConcept	0..*	Level of occurrence of the DNA variation in relation to the genomic context. LOINC answer list: LOINC 53034-5
Subject[3]	Patient	1	Genetic laboratory's patient identification for this sequence
Specimen[3]	Specimen	1	Specimen source of data
Interpretation[3]	CodeableConcept	0..*	Interpretation of the effect of this observation. Uses "Observation Interpretation Codes" value set of FHIR.
Comment[3]	String	0..*	Comments on this variant

HL7_DAM_CLINSEQ_R1_INFORM_2017FEB

HL7 Domain Analysis Model: Clinical Sequencing, Release 1

February 2017

HL7 Informative Document

Sponsored by Clinical Genomics Work Group (CGWG)
Co-Chairs: Gil Alterovitz, Mollie Ullman-Cullere, Bob Milius, Amnon Shabo (Shvo)

Questions or comments regarding this document should be directed to Gil Alterovitz at ga@alum.mit.edu or Mollie Ullman-Cullere at mollie.ullmancullere@gmail.com

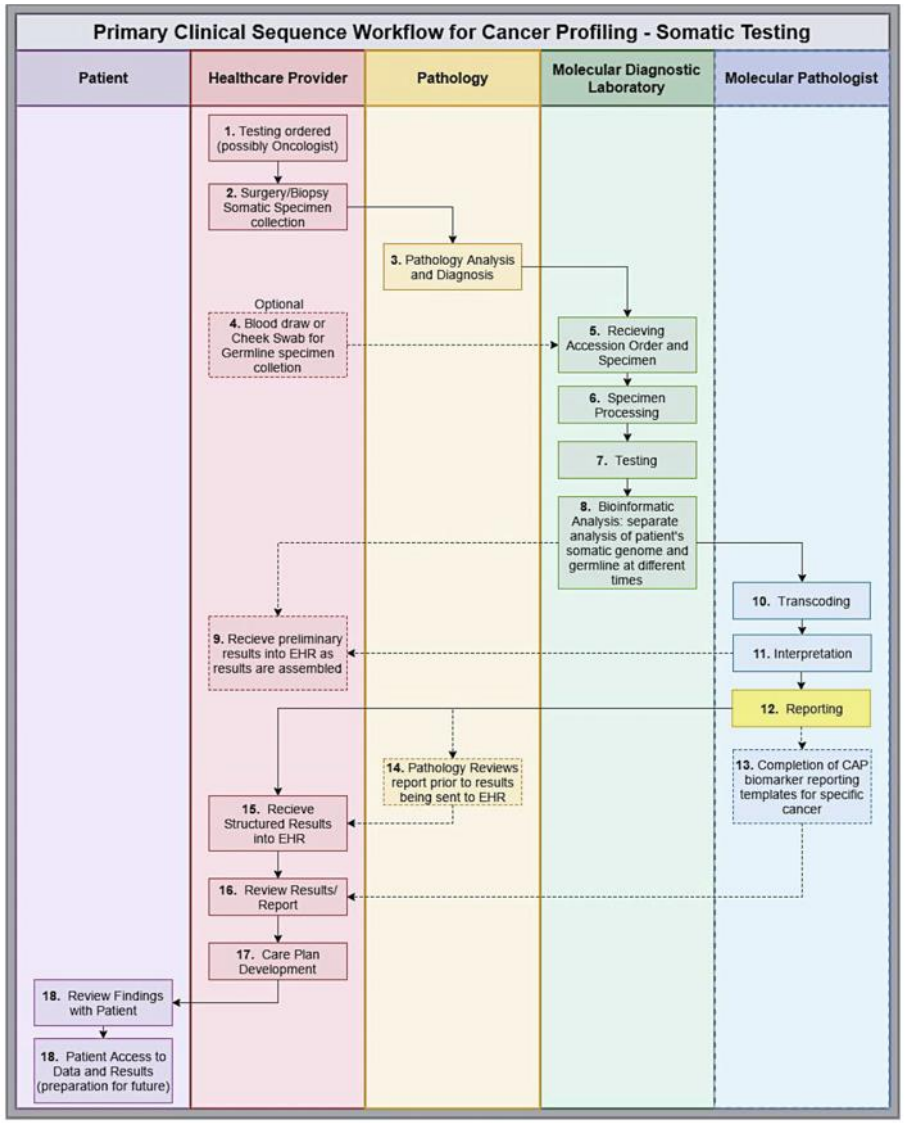
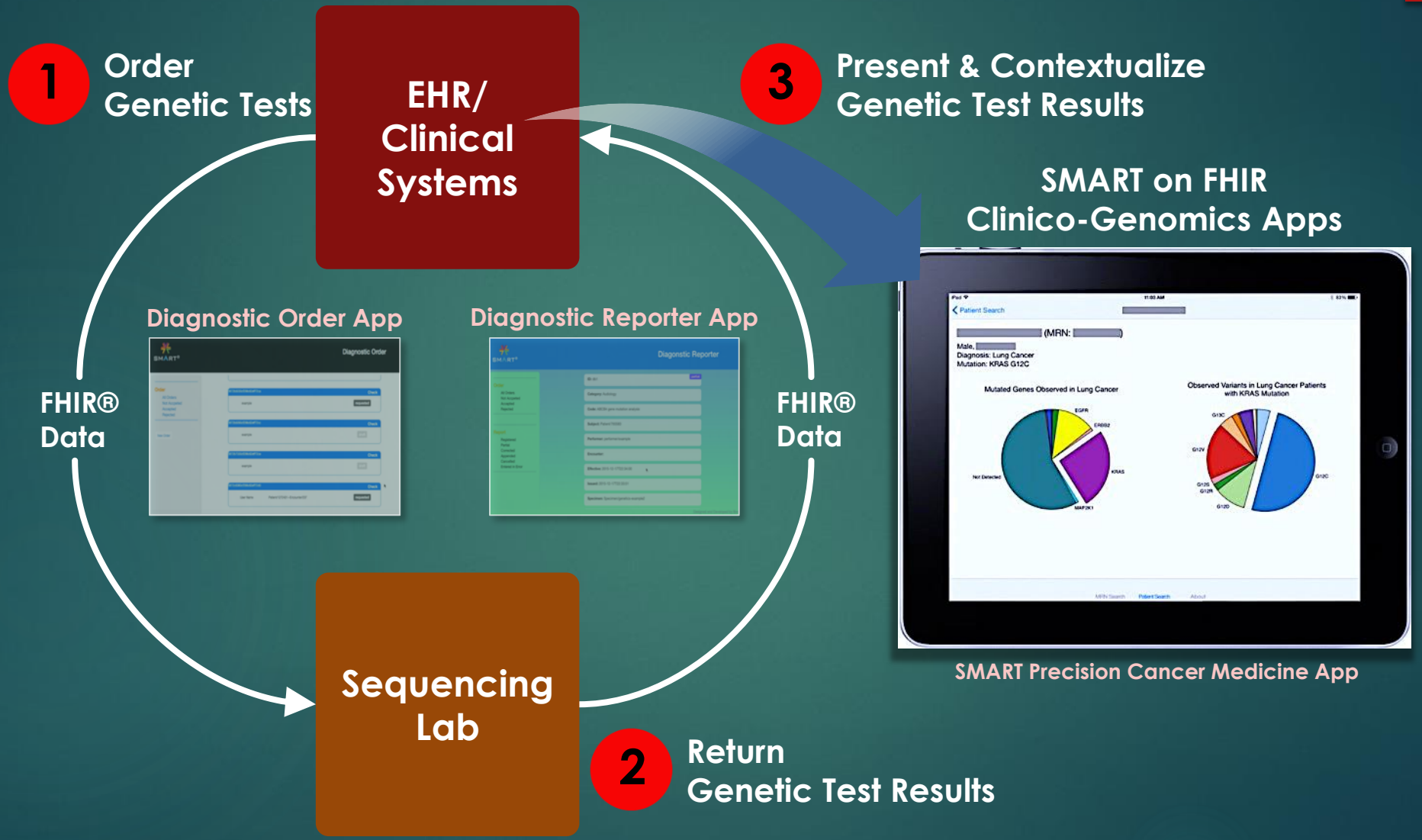


Figure 5.3-1: General workflow of somatic testing: 1. Sequence testing is ordered either by a physician or by an oncologist. 2. Suspected tumorigenic cells are identified and a specimen is collected by a clinician/surgeon. 3. The somatic specimen is sent to pathology where it is tested and analyzed for proper diagnosis. 4. (Optional) Blood is drawn or cheek swabbed for cells containing DNA for germline testing. 5. Laboratory receives specimen(s) and an order for genetic testing, including relevant data to aid in evaluation and interpretation of findings: indication for testing, cancer type, and relevant clinical/pathological data for the patient.

Standards-enabled workflow



Warner et al. doi: 10.1186/s13073-016-0371-3

Improving Cancer-Related Outcomes with CONNECTED HEALTH

A Report to the President of the United States from the President's Cancer Panel

Precision Cancer Medicine App Helps Oncologists Use Genomic Information

Genomic data increasingly are informing treatment decisions for cancer patients and those at risk for cancer, but commercially available EHRs generally cannot display clinical genomic data in meaningful ways. The Precision Cancer Medicine (PCM) app was designed to present patients' genomic test results to oncologists in real time as a component of clinical practice, as well as provide links to external knowledge bases that otherwise would be unavailable through the native EHR system. PCM was piloted at Vanderbilt University and integrated into that institution's EHR system. However, because the app was developed based on an open-access API (Substitutable Medical Applications and Reusable Technology, or SMART) and uses the emerging HL7 Fast Healthcare Interoperability Resources standard, it could easily be deployed for other compatible EHR systems.

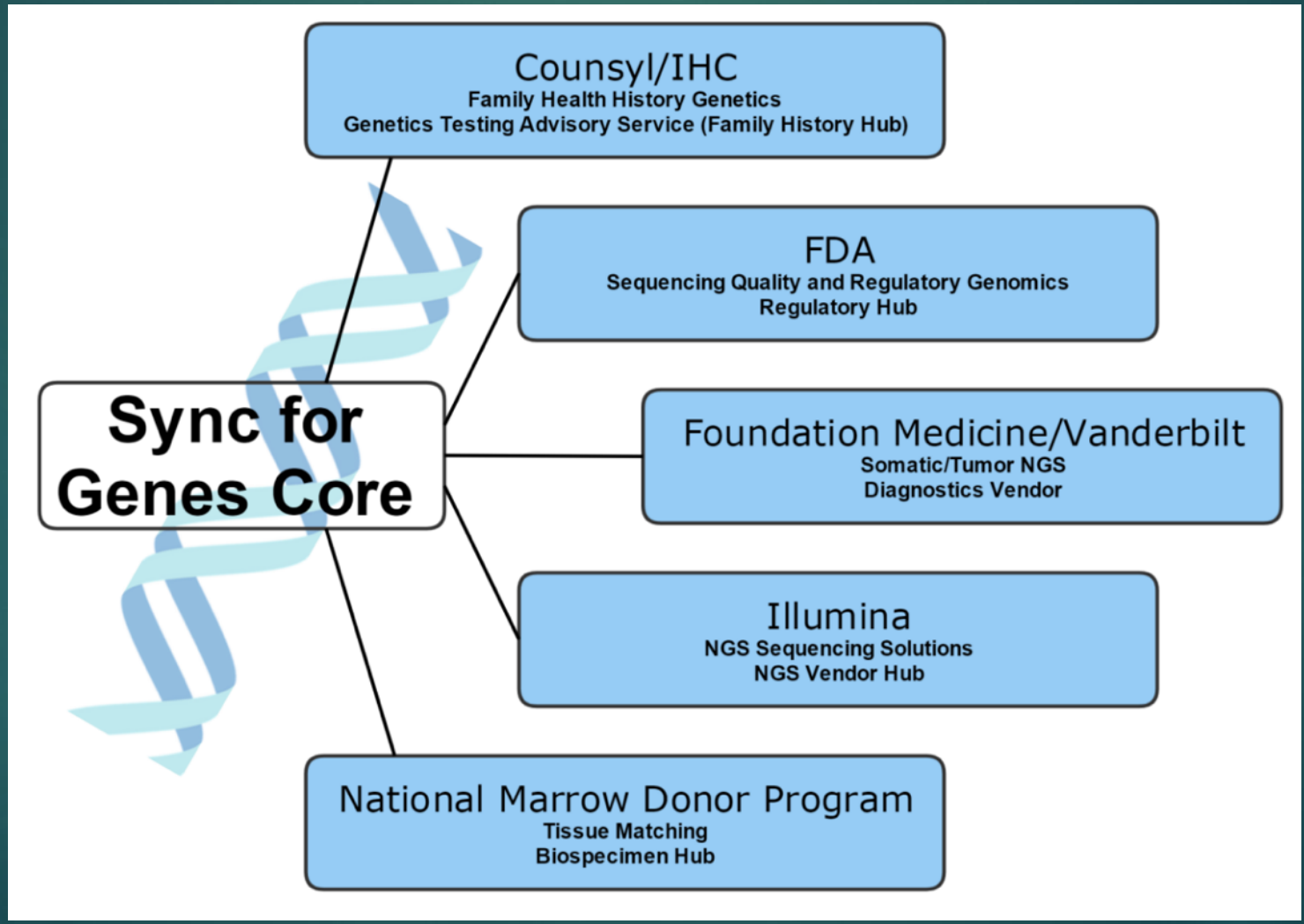
Sources: Mandel JC, Kreda DA, Mandl KD, Kohane IS, Ramoni RB. SMART on FHIR: a standards-based, interoperable apps platform for electronic health records. J Am Med Inform Assoc. 2016;23(5):899-908; Warner JL, Rioth MJ, Mandl KD, Mandel JC, Kreda DA, Kohane IS, et al. SMART precision cancer medicine: a FHIR-based app to provide genomic information at the point of care. J Am Med Inform Assoc. 2016;23(4):701-10.

Action Item 3.3

Develop and test tools and interfaces, including apps, tailored to needs of the oncology workforce.

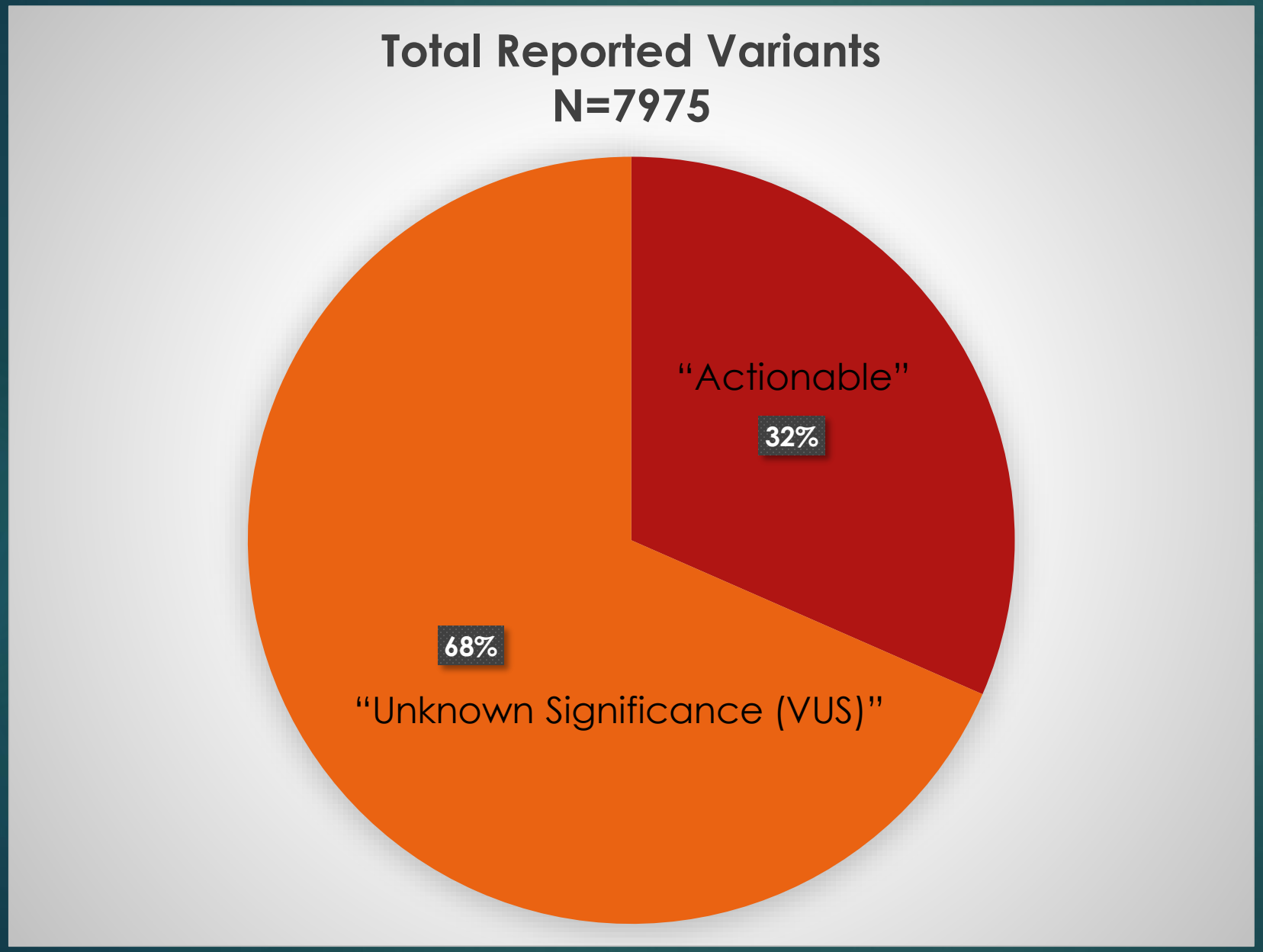
https://prescancerpanel.cancer.gov/report/connectedhealth/

Sync for Genes: Bringing genomic knowledge into the workflow



https://www.healthit.gov/sites/default/files/sync_for_genes_report_november_2017.pdf

Why we need knowledge bases I



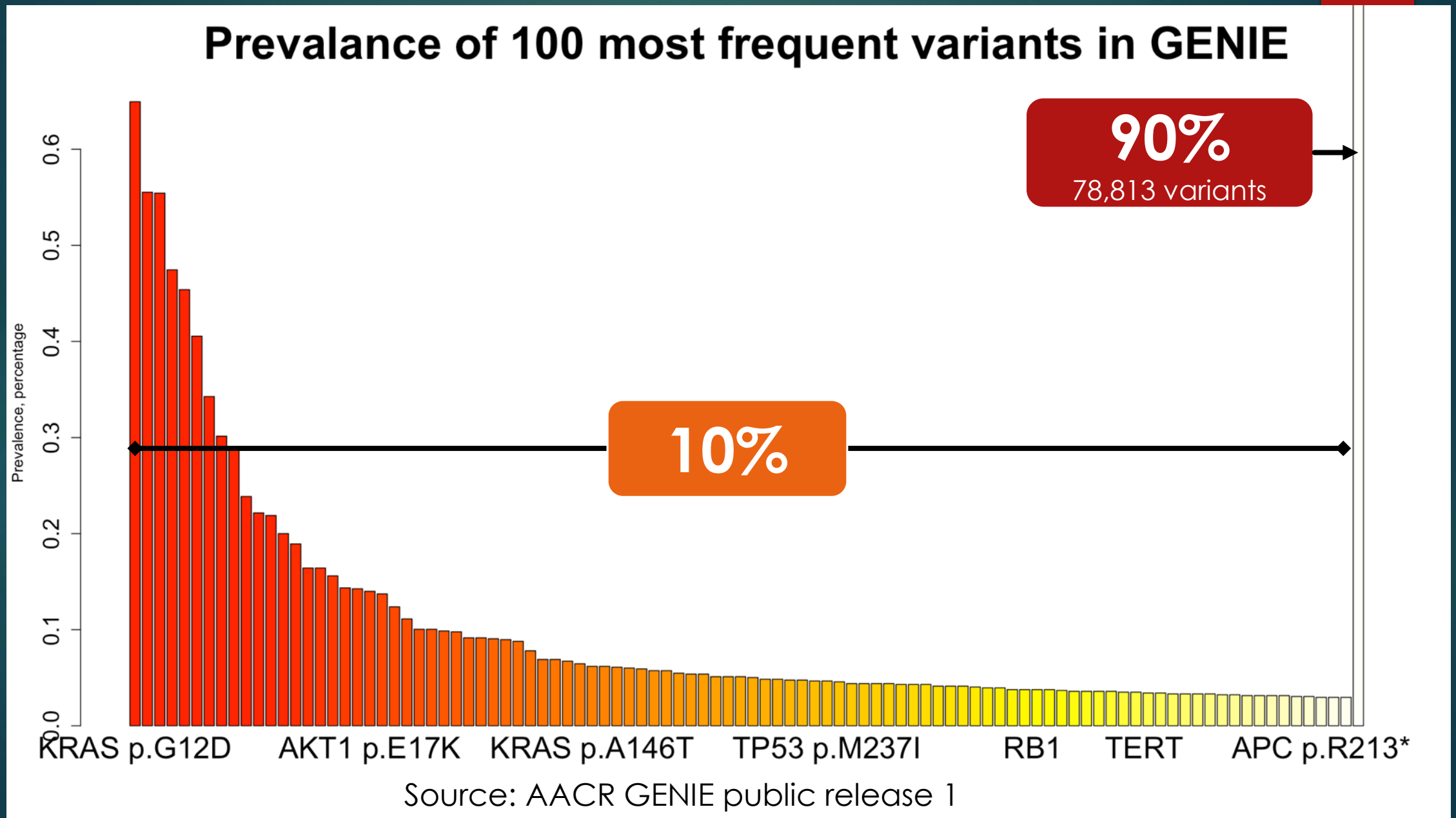
Median "actionable" variant per patient:

4

Median VUS per patient:

7

Why we need knowledge bases II



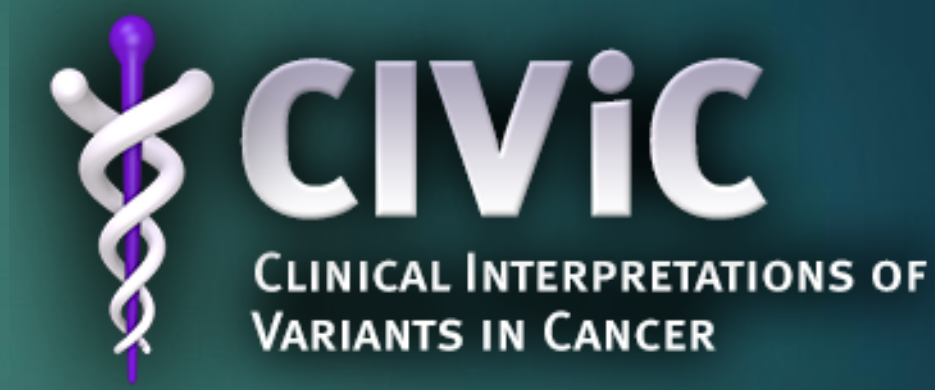
Source: AACR GENIE public release 1

Precision oncology knowledge bases (a sampling)

Micheel et al. doi: 10.1016/j.cancergen.2014.06.016

Chakravarty et al. doi: 10.1200/PO.17.00011

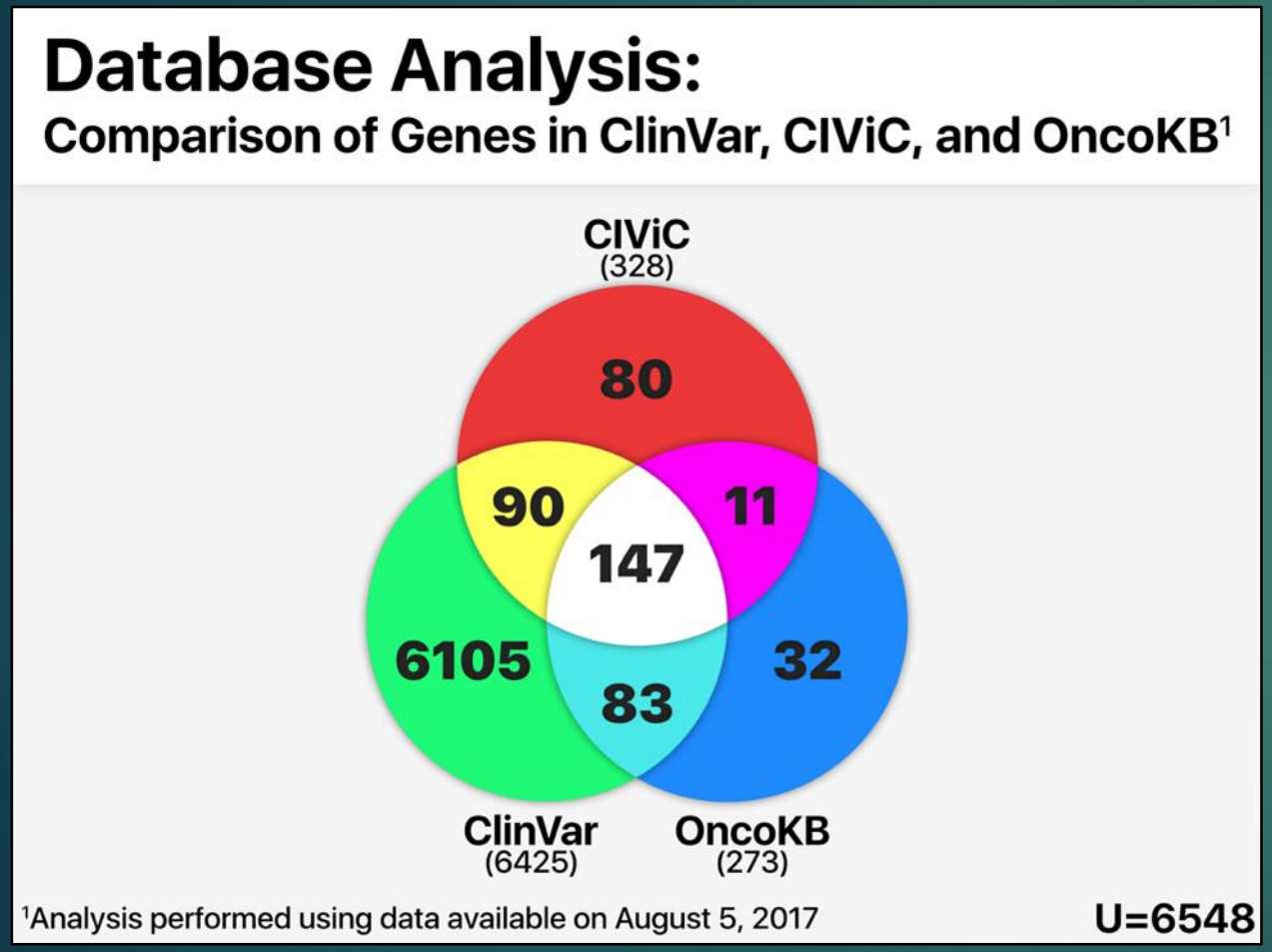
Huang et al. doi: 10.1093/jamia/ocw148

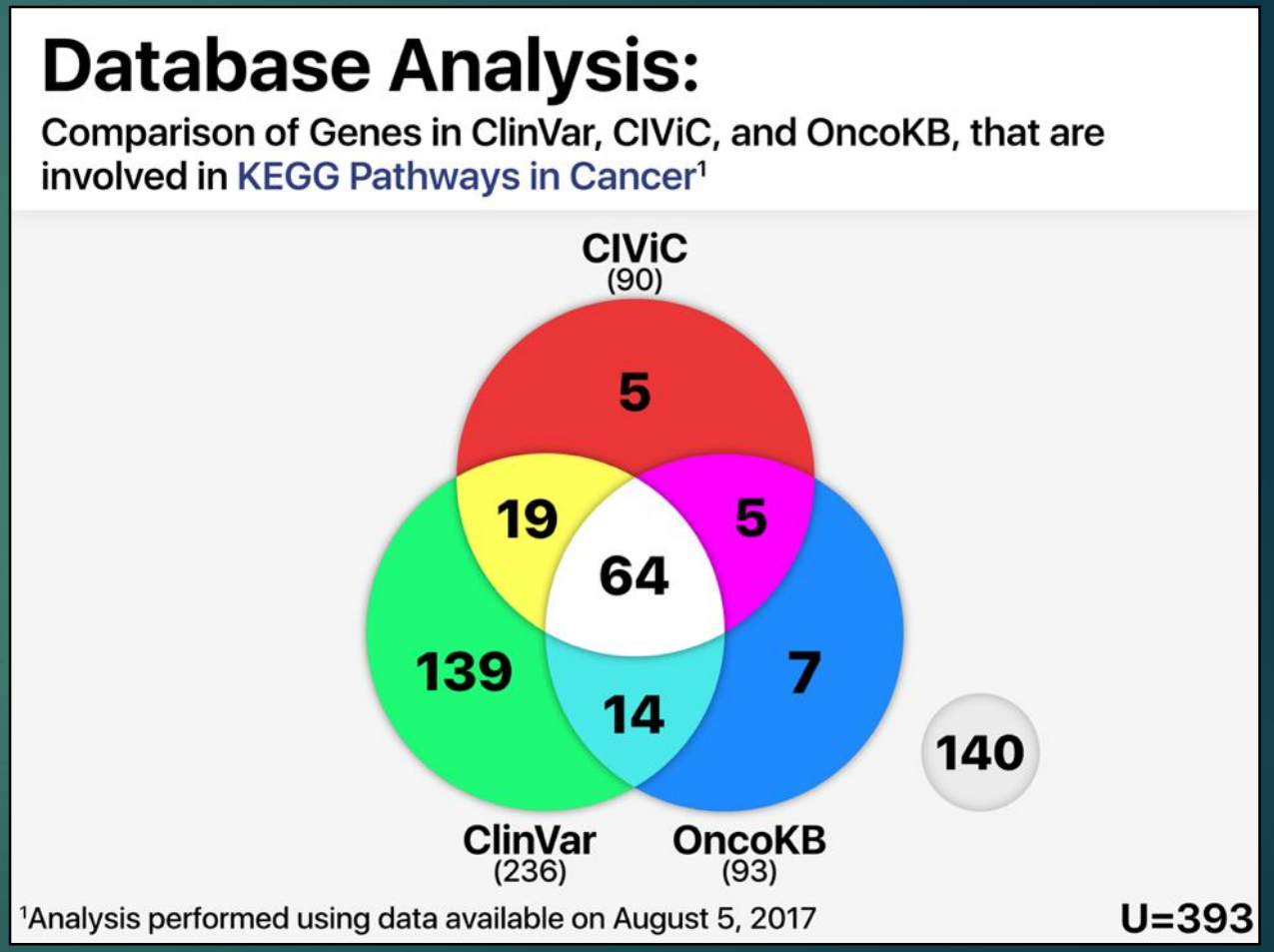


Griffith et al. doi: 10.1038/ng.3774

Patterson et al. doi: 10.1186/s40246-016-0061-7

Unequal database coverage





Warner et al. accepted for publication

The problem in a nutshell – Representative interpretations from 3 knowledge bases use a variety of custom nomenclature, ontologies, etc

OncoKB

Gene: BRAF (Entrez: 673)
Isoform: ENST00000288602 RefSeq: NM_004333.4
Variant: V600E (????)
Disease: Melanoma (oncotree)
Drug: Dabrafenib
knownEffect: Sensitive
Level: 2B
ApprovedIndications: Dabrafenib is FDA-approved for BRAF V600E mutant unresectable or metastatic melanoma.

CIViC
Clinical Interpretations of Variants in Cancer

Gene: BRAF (Entrez: 673)
Isoform: ENST00000288602.6
Variant: V600E (chr7:g.140453136A>T)
Disease: Skin Melanoma (DOID:8923)
Drug: Dabrafenib + Trametinib
Clinical Significance: Sensitivity
Level: A – Validated
Evidence statement: Open-label, randomized phase 3 trial with 704 patients with metastatic melanoma with a BRAF V600 mutation. Patients were randomized ...

Weill Cornell Medical College Cornell University
PMKB

Gene: BRAF (???)
Isoform: ENST00000288602
Variant: V600E (7:140453136-140453136)
Tumor: Melanom; Tissue: Skin
Drug: ???
Clinical Significance: ???
Tier: 1
Evidence statement: ... Various B-Raf inhibitors(Vemurafenib, Dabrafenib) have been FDA approved for melanoma therapy in certain settings.

Global Alliance
for Genomics & Health

Collaborate. Innovate. Accelerate.

Variant Interpretation for Cancer Consortium (VICC)

www.cancervariants.org

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Identifying Health Information Technology Needs of Oncologists to Facilitate the Adoption of Genomic Medicine:

Key recommendations of the ASCO Omics and Precision Oncology workshop:

1.	The development of genomic CDS tools is essential as **genomics knowledge is growing beyond human capabilities**.
2.	Standards development organizations should rapidly produce generally accepted, **comprehensive standards** for transmitting genomic information and should closely collaborate to avoid discrepancies between competing standards. Naming conventions for genes and genomic abnormalities should be **harmonized and should be accepted by all** except in the most exceptional of circumstances.
3.	A software application (app) should be developed by or on behalf of ASCO, to help both community and academic oncologists integrate higher quality genomic data into clinical practice.
4.	The **content of all freely available genomic knowledge bases should be made available via APIs**, to ensure that apps can be developed to take advantage of their carefully curated content in an automated manner. Genomic knowledge bases should conform to FDA guidance and should have clinical trial links or pass-throughs to the ClinicalTrials.gov API.

Hughes et al. doi: 10.1200/JCO.2017.74.1744

Take-home points

- Genomics will become increasingly relevant to cancer care before, during, and after diagnosis
- Without agreed-upon standards, we will not be able to build large datasets that inform cancer diagnosis, prognosis, and treatment
- Given the vast breadth of knowledge, artificial intelligence and machine learning will be critical to the practice of precision oncology

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- Obi Griffith (VICC)
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* Directly involved in programming of SMART PCM