NCCN 2021 Virtual Congress:
Biomarkers in Solid Tumors

Friday, November 12, 2021
11:10 AM – 11:55 AM EST

General Principles of Test Interpretations:
What Results are Actionable and How to Advise Patients About Results?

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University of Colorado Cancer Center

National Comprehensive Cancer Network®

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Learning Objectives

- Describe the benefits and limitations of companion diagnostic and alternative tests
- Review ways to decipher laboratory reports and understand pitfalls and limitations of genomic test results
- Describe how the tiered reporting systems can be used to prioritize results
- Name web resources that can be used to obtain information about complex variants

Overview

- Types of tests
  - Regulatory perspective
  - Technology perspective
- Types of results

Types of Tests: Regulatory Perspective

- Laboratory medicine is subject to regulation through CLIA ’88, which has many stipulations about testing
- Testing developed by manufacturers and distributed to laboratories is additionally subject to FDA approval
  - These are treated as medical devices (like a pacemaker)
- Currently there is debate about the role of FDA in regulation of laboratory testing that is not distributed by a manufacturer

42 CFR 493.1253 - Standard:
Establishment and verification of performance specifications
(2) Establishment of performance specifications. Each laboratory that …. or introduces a test system ….must, before reporting patient test results, establish …. the **performance specifications** for the following performance characteristics, **as applicable**:
(i) Accuracy.
(ii) Precision.
(iii) Analytical sensitivity.
(iv) Analytical specificity to include interfering substances.
(v) Reportable range of test results for the test system.
(vi) Reference intervals (normal values).
(vii) Any other performance characteristic required for test performance

Different ‘Dx’ Assays – what does this mean?

Testing Type	Pros	Cons
Companion Diagnostic (CDx)	• Specifically associated with responsiveness in trial • FDA Approved for that specific indication • Considered mandatory for drug utilization in indication	• Can be limited to specific variants, locked in testing methodology • Difficult to add new targets • May compromise ability to perform other tests (e.g. tissue utilization)
Complementary Diagnostic	• Applies to a class of assays and therefore a single specific assay not needed, can apply to a class of drug • Considered optional	• Not many of them • Mostly in IHC space
Laboratory Developed Test (LDT)	• Greatest degree of flexibility to update testing • Optimized for specimen types typical to a specific population	• Perception that they are unreliable (I disagree!) • Thresholding at or near decision cut-points may differ from CDx

Most oncology NGS today is LDT

Different Viewpoints on LDTs

JAMA February 17, 2015 Volume 313, Number 7

VIEWPOINT

Genetic Testing and FDA Regulation
Overregulation Threatens the Emergence of Genomic Medicine

AJCP / Review Article

Regulation of Laboratory-Developed Tests

A Clinical Laboratory Perspective

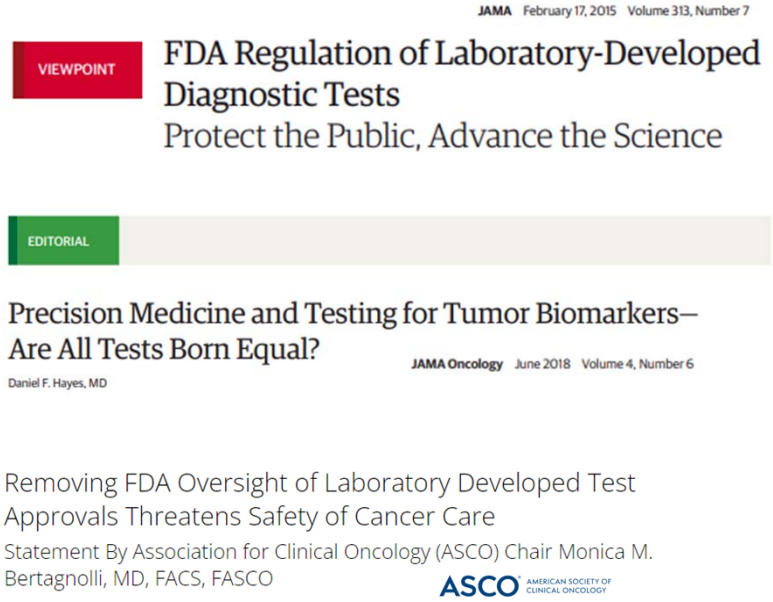
Jonathan R. Genzen, MD, PhD[1,2]

From the [1]Department of Pathology, University of Utah, Salt Lake City; and [2]ARUP Laboratories, Salt Lake City, UT.

A High-Level Overview of the Regulations Surrounding a Clinical Laboratory and Upcoming Regulatory Challenges for Laboratory Developed Tests

Kevin C. Graden, MS, Shannon A. Bennett, MS, MBA, Sarah R. Delaney, PhD, Hillary E. Gill, BS, Maria A. V. Willrich, PhD

Laboratory Medicine 2021;52:315-328



JAMA February 17, 2015 Volume 313, Number 7

VIEWPOINT

FDA Regulation of Laboratory-Developed Diagnostic Tests
Protect the Public, Advance the Science

EDITORIAL

Precision Medicine and Testing for Tumor Biomarkers—Are All Tests Born Equal?

JAMA Oncology June 2018 Volume 4, Number 6

Daniel F. Hayes, MD

Removing FDA Oversight of Laboratory Developed Test Approvals Threatens Safety of Cancer Care

Statement By Association for Clinical Oncology (ASCO) Chair Monica M. Bertagnolli, MD, FACS, FASCO

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Overview

- Types of tests
  - Regulatory perspective
  - Technology perspective
- Types of results

Technical Elements ALWAYS Underlie Interpretation

- Interpretation of any test without knowing something about the technology has risks
- The technology platform selected for a test influences:
  - The spectrum of results obtained
  - The confidence for detection of low level mutations
    - Which may be very meaningful if a sample has low tumor content
  - The ability to detect less common events like fusions

Major things to know about testing:

- What type of sample was tested?
- Was tumor enrichment utilized?
- What testing methodology was utilized?
- What are the major 'gaps' in that method?
- Are those gaps worth pursuing?

The Most Important Thing…

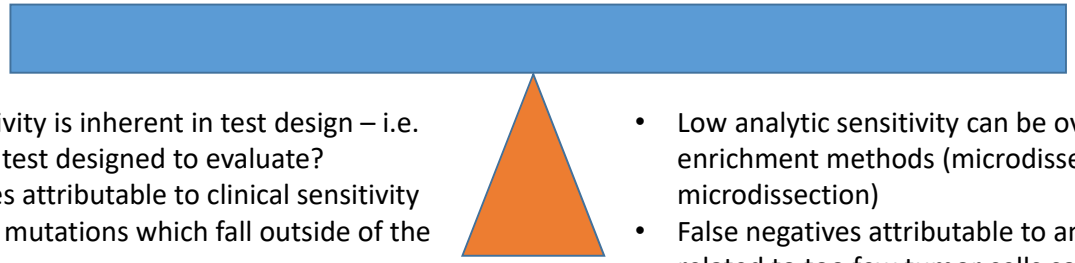
No Test Is Perfect

- Every test has ‘holes’
- It’s important to know what they are!

Methods for Mutation Testing: A Balancing Act

Clinical Sensitivity:
How many of the possible changes does the test detect?

Analytic Sensitivity:
How sensitively can the test detect a rare change in a background of normal? [LOD]



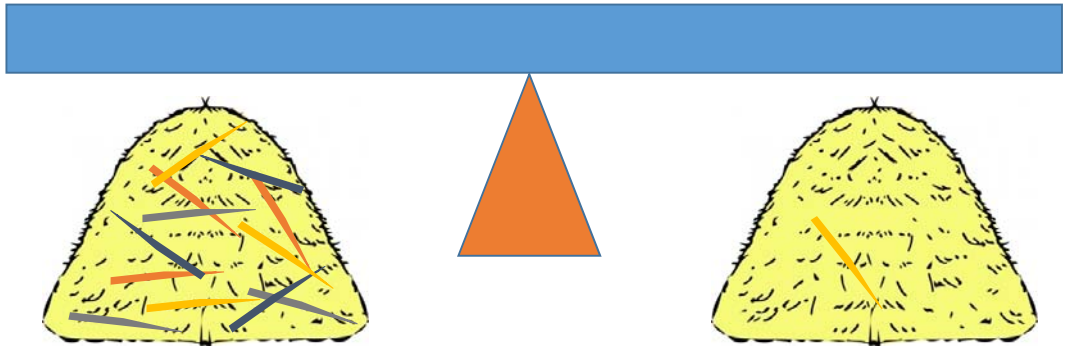
- Clinical sensitivity is inherent in test design – i.e. what was the test designed to evaluate?
- False negatives attributable to clinical sensitivity are related to mutations which fall outside of the test design
- Example: *EGFR* test which picks up only L858R and Exon 19 deletions will not detect Exon 20 insertions

- Low analytic sensitivity can be overcome with tumor enrichment methods (microdissection, laser capture microdissection)
- False negatives attributable to analytic sensitivity are related to too few tumor cells compared to non-tumor (or rare sub-clone with mutation)
- Example: Pleural fluid cell block, with many more reactive mesothelial cells than tumor cells, difficult to enrich

In English…

Clinical Sensitivity:
How many of the possible changes does the test detect?

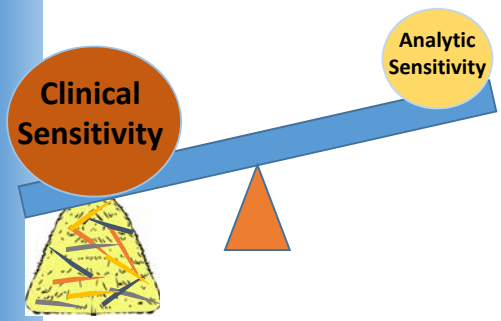
Analytic Sensitivity:
How sensitively can the test detect a rare change in a background of normal? [LOD]

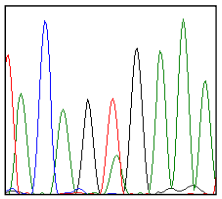


Looking for a needle in a haystack
- The test can identify needles of many different colors, but need to exist at a relatively high level

Looking for a needle in a haystack
- The test can identify only a couple of colors of needles, but can pick them out even when they are very rare

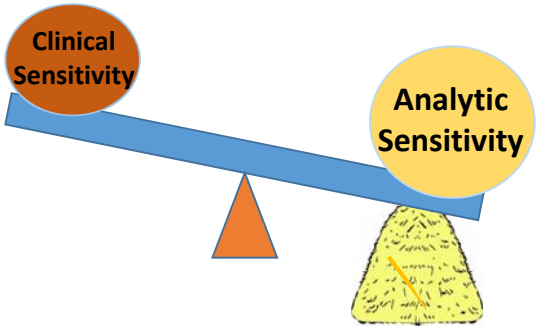
Sanger Sequencing

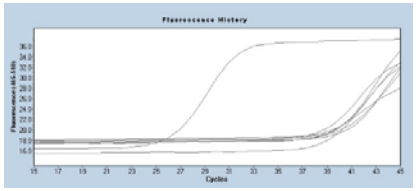




Problematic LOD for many applications

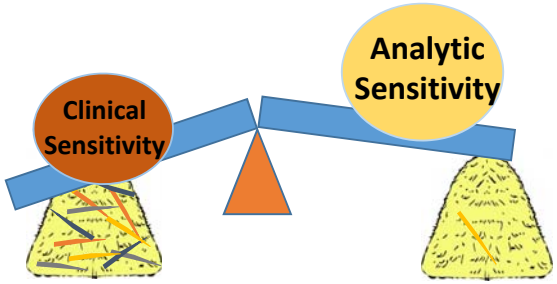
qPCR

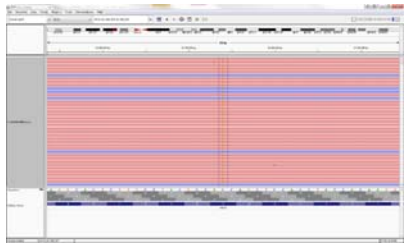




Highly targeted – only asks limited questions

NGS





Good middle ground on both of these
NGS can be modulated to have ultra-sensitive detection

NGS: A Platform

- NGS is a platform not a test
- How the NGS test is designed will dictate what it can and can't tell you
- Things to think about:
  - What genes are on the panel?
  - What kinds of alterations can the assay detect?
  - What are the known weak spots for how the assay is designed?

Type of NGS Test	Features/Scope

Targeted Mutation Assay	• Can be performed on FFPE or blood
	• Mutations in a set of genes
	  • Can be 3 to hundreds of genes and will vary
	  • May not evaluate for amplifications, fusions

Exome	• Evaluates all coding genes (~20,000 genes) • Typically does not cover fusions
Transcriptome	• Evaluates all expressed genes • Typically covers fusions • Ability to detect rare events may be compromised

Overview

- Types of tests
  - Regulatory perspective
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Types of Results: The Traditional View

- Classify by the type of genomic alteration, e.g.:
  - Point mutations
  - In/del mutations
  - Copy number changes
  - Structural changes (e.g. rearrangements/fusions)
  - Mutational burden
  - Microsatellite instability
- Each one of these has a cognate cohort of therapies to choose from
  - *In the appropriate context of the specific alteration*
  - *And specific disease*

Types of Alterations: The Traditional View

- Specific Alterations:
  - *BRAF* p.V600E
  - *EGFR* p.L858R
  - *METex14* skip
  - *ERBB2* amplification
  - *NTRK1/2/3* fusion
  - etc

→ Is the tumor type:
Thyroid
NSCLC
Melanoma
CRC

→ Y →

There is an FDA approved and/or guideline-recommended therapy

Types of Alterations: The Traditional View

- Specific Alterations:
  - *BRAF* p.V600E
  - *EGFR* p.L858R
  - *METex14* skip
  - *ERBB2* amplification
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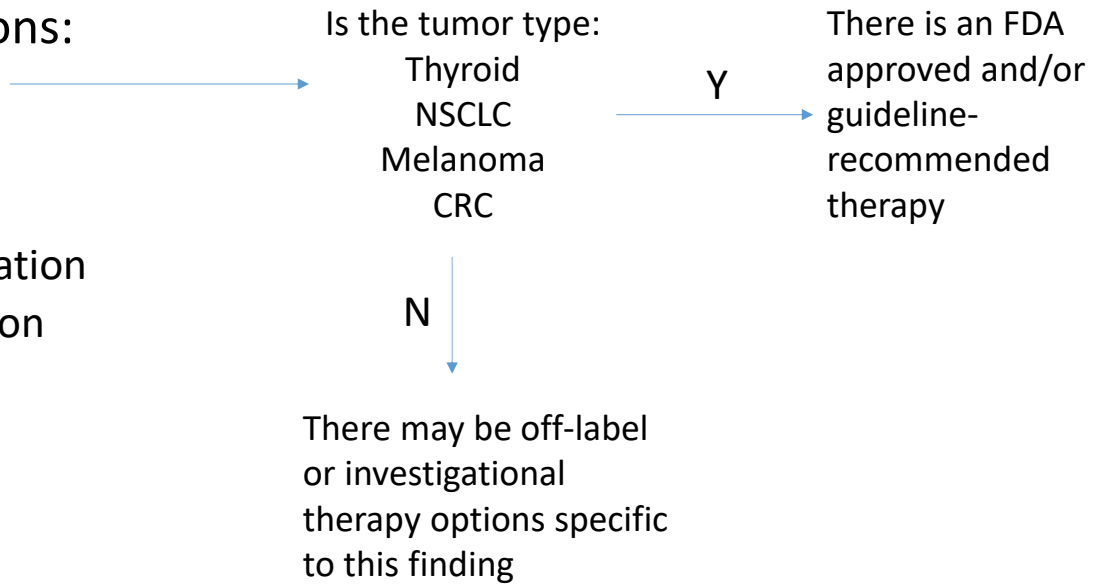
  - etc



Types of Alterations: The Traditional View

Tier I: Variants of Strong Clinical Significance

Therapeutic, prognostic & diagnostic

Level A Evidence

FDA-approved therapy

Included in professional guidelines

Level B Evidence

Well-powered studies with consensus from experts in the field

Tier II: Variants of Potential Clinical Significance

Therapeutic, prognostic & diagnostic

Level C Evidence

FDA-approved therapies for different tumor types or investigational therapies

Multiple small published studies with some consensus

Level D Evidence

Preclinical trials or a few case reports without consensus

Tier III: Variants of Unknown Clinical Significance

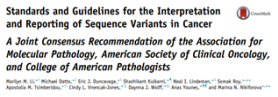
Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases

No convincing published evidence of cancer association

Tier IV: Benign or Likely Benign Variants

Observed at significant allele frequency in the general or specific subpopulation databases

No existing published evidence of cancer association


Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

Types of Alterations: The Traditional View

ESMO

Annals of Oncology 29: 1895–1902, 2018
doi:10.1093/annonc/mdy263
Published online 21 August 2018

SPECIAL ARTICLE

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J.-Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12]* & L. Pusztai[13]

Table 2. The ESCAT

	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcome in clinical trials	I-A: prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point I-B: prospective, non-randomised clinical trials show that the alteration-drug match in a specific tumour type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1 I-C: clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care
Investigational	II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	II-A: retrospective studies show patients with the specific alteration in a specific tumour type experience clinically meaningful benefit with matched drug compared with alteration-negative patients II-B: prospective clinical trial(s) show the alteration-drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival end points	Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumour type, but additional data are needed	Treatment to be considered 'preferable' in the context of evidence collection either as a prospective registry or as a prospective clinical trial
Hypothetical target	III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration	III-A: clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumour type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types III-B: an alteration that has a similar predicted functional impact as an already studied tier I abnormality in the same gene or pathway, but does not have associated supportive clinical data	Drug previously shown to benefit the molecularly defined subset in another tumour type (or with a different mutation in the same gene), efficacy therefore is anticipated for but not proved	Clinical trials to be discussed with patients
	IV: pre-clinical evidence of actionability	IV-A: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical *in vitro* or *in vivo* models IV-B: actionability predicted *in silico*	Actionability is predicted based on preclinical studies, no conclusive clinical data available	Treatment should 'only be considered' in the context of early clinical trials. Lack of clinical data should be stressed to patients
Combination development	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome	Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation	Clinical trials assessing drug combination strategies could be considered
	X: lack of evidence for actionability	No evidence that the genomic alteration is therapeutically actionable	There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target	The finding should not be taken into account for clinical decision

What is NOT a Mutation?*

* from a clinical perspective for somatic changes

- Single Nucleotide Polymorphism(s)
  - Benign** changes in the genome
  - Everyone carries lots of SNPs
  - In molecular genetics, we define a SNP as any alteration that has a prevalence of ≥ 1% minor allele fraction in any population**
  - How do we decide what is a SNP?
    - We use databases – there are lots of them!

** There are exceptions

TP53 c.215C>G; p.P72R

gnomAD browser

Population Frequencies

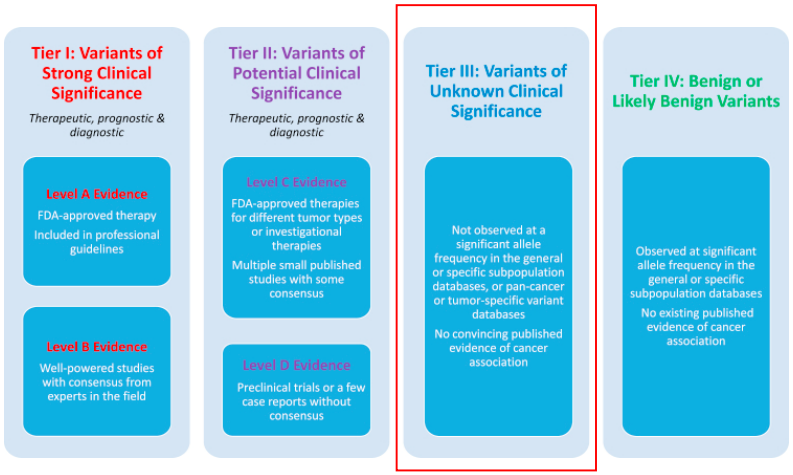
Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (non-Finnish)	94889	128822	34940	0.7366
European (Finnish)	18300	25100	6645	0.7291
Ashkenazi Jewish	7414	10366	2641	0.7152
Latino/Admixed American	25286	35416	9030	0.7140
Other	4999	7178	1753	0.6964
East Asian	11314	19918	3235	0.5680
South Asian	15313	30614	3897	0.5002
African/African-American	9317	24432	1785	0.3813
XX	85910	128672	29624	0.6677
XY	100922	153174	34302	0.6589
Total	**186832**	**281846**	**63926**	**0.6629**

- Some of these have debatable biologic function
- Many studies about SNPs serving as modifiers of disease
- Currently, most labs filter these out…so you will not see them…
- Why should you care, then?

- In tumor-only NGS testing:
  - Hundreds or thousands of variants are identified per person
  - We use databases to filter out anything that meets criteria as a SNP
- BUT…
  - SNP databases are only as good as the populations that are represented
  - Means ethnically under-represented groups could have true SNPs overcalled

SNP Filtering and VUS

- Filtering of SNPs impacts what variants show up here:



Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

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VUS

= Variant of Uncertain Significance

- Patient reports may have variants listed which are benign/SNP
  - If not in databases as a SNP/benign, will be called a VUS
  - 'Private' polymorphism – benign change that does not have significant population frequency
- Don't be misled by these – anything that is classified as VUS implies insufficient evidence exists to make a data-based treatment decision
  - Even if it's in a gene that is known to impact therapy selection
  - Example:

    EGFR c.2170G>A; p.P848L
    In between known activating mutations
    Not an indication for first-line TKI

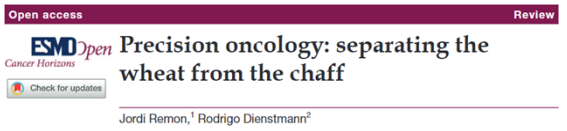
Tiering (in some fashion) is how you are likely to see molecular results

- May tier based on
  - Published guidelines
  - CDx status
  - Separate strategy
- = know how to read the report (regardless of the tiering structure)


Recommendations for designing genetic test reports to be understood by patients and non-specialists

George D. Farmer[1,2] · Harry Gray[1,3,4] · Gemma Chandratillake[5,6] · F Lucy Raymond[5,7] · Alexandra L. J. Freeman[1]

European Journal of Human Genetics (2020) 28:885–895
https://doi.org/10.1038/s41431-020-0579-y


Open access Review

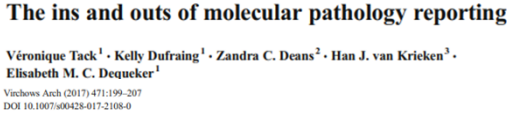
ESMO Open Cancer Horizons

Precision oncology: separating the wheat from the chaff

Jordi Remon,[1] Rodrigo Dienstmann[2]

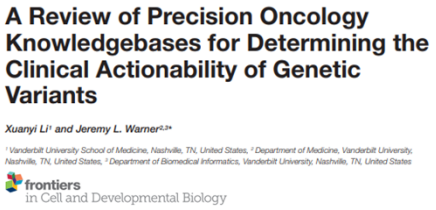

Clinical Use of Precision Oncology Decision Support

ascopubs.org/journal/po JCO™ Precision Oncology


The ins and outs of molecular pathology reporting

Véronique Tack[1] · Kelly Dufraing[1] · Zandra C. Deans[2] · Han J. van Krieken[3] · Elisabeth M. C. Dequeker[1]

Virchows Arch (2017) 471:199–207
DOI 10.1007/s00428-017-2108-0


A Review of Precision Oncology Knowledgebases for Determining the Clinical Actionability of Genetic Variants

Xuanyi Li[1] and Jeremy L. Warner[2,3]*

[1] Vanderbilt University School of Medicine, Nashville, TN, United States, [2] Department of Medicine, Vanderbilt University, Nashville, TN, United States, [3] Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, United States

frontiers in Cell and Developmental Biology


TECHNICAL REPORT
https://doi.org/10.1038/s43018-021-00243-3
nature cancer

OPEN

Integrating molecular profiles into clinical frameworks through the Molecular Oncology Almanac to prospectively guide precision oncology

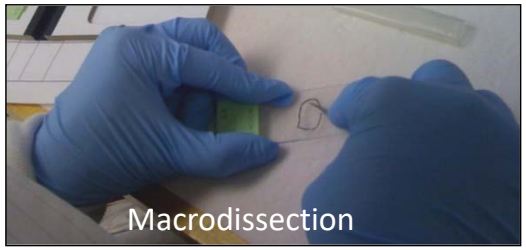
Pitfalls and Landmines: VUS

= Variant of Uncertain Significance

- Many labs have a separate section of the report for these variants
- In general, these are NOT actionable
- But that doesn't mean you shouldn't review them

- Examples:
  - Some things that truly *are* VUS are in the main part of the report
    - Examples: *ROS1* amplification, *NTRK1/2/3* point mutations
    - Some labs will put anything that *might* be biologically important into the 'top' part of the report
    - Other labs may put anything without *definitive* biological/therapeutic impact into the VUS section
  - Rarely, something important might get misclassified as VUS

Pitfalls and Landmines: Tumor Enrichment
(and methodology)


Macrodissection

Microdissection

Tumor enrichment approaches are variable
No enrichment vs. macrodissection vs. microdissection:

5. Does your laboratory use macrodissection or microdissection to enrich cell populations before testing?	No. labs (133)
Laser capture microdissection (LCM)	-
Manual microdissection (H&E slide is examined and marked by a pathologist for subsequent tumor dissection under the light microscope)	26
Macrodissection (H&E slide is examined and marked by a pathologist for subsequent tumor dissection without microscope)	89
Do not use micro or macrodissection (whole tissue used for analysis)	18

Increasing risk for FN

CAP Proficiency testing participant summary (KRAS-B-2020)

Pitfalls and Landmines: Amplification

- Some NGS tests don't do a great job of distinguishing a true amplification from a whole chromosome gain
- NGS tests best detect amplification when it is based in a copy number >6
  - This means that true amplifications with lower copy number won't be detected
  - Example: Breast carcinoma with FISH defined amplification of:
    - *ERBB2/HER2* copies per cell: 5
    - *CEP17* copies per cell: 2
    - Ratio = 2.5

Sensitivity Study for *ERBB2* Amplification Detection

Sample	Dilution (%)	*ERBB2* fold change	Result
FFPE (HER2/CEP17, 13.7)	100	49.38	AMP called
	50	14.44	AMP called
	25	6.90	AMP called
	12.50	3.73	AMP called
	6.25	2.34	AMP called
	3.13	1.56	AMP called
MDA-MB-361 (HER2/CEP17, 4.2)	100	5.66	AMP called
	50	3.32	AMP called
	25	2.16	AMP called
	12.50	1.61	AMP called
	6.25	1.33	AMP not called
MDA-MB-453 (HER2/CEP17, 2.4)	100	2.31	AMP called
	50	1.61	AMP called
	25	1.3	AMP not called
	12.50	1.15	AMP not called
	6.25	1.0	AMP not called

Ross et al. J Mol Diagn. 2017.

Pitfalls and Landmines: Tiering Based on CDx

- Look for alterations in the non-CDx section!
- CDx sections of an NGS report are a regulatory designation
  - It means that the test is FDA-approved for the specific alteration in a specific tumor type
  - But it is not everything that could have a clinical implication

Example from a real report:

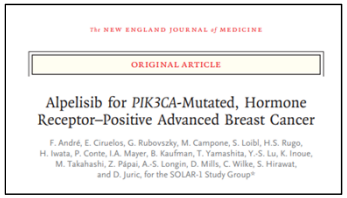
In the 'CDx' section of the report:	'No reportable alterations with Companion Diagnostic Claims'	
In the 'Other Biomarkers' section of the report:	'*CD74-ROS1* Fusion identified'	This is a regulatory distinction Not a biologic distinction

Pitfalls and Landmines: Drugs Based on CDx

- Assays with FDA approved CDx indication may list a drug for an identified target
  - But it will only list the drug with which the CDx is associated
  - Example:
    - *NTRK3* fusion detected
    - Which drug is listed in the report will depend on which test it is!

Pitfalls and Landmines: Targeted CDx Assays

- Example: *PIK3CA* mutation testing in breast cancer
- Targeted CDx (real-time PCR) for this mutation-drug combo detects:
  - p.C420R
  - p.E542K/A/D
  - p.E545G/K/E
  - p.Q546R
  - p.H1047L/R/Y



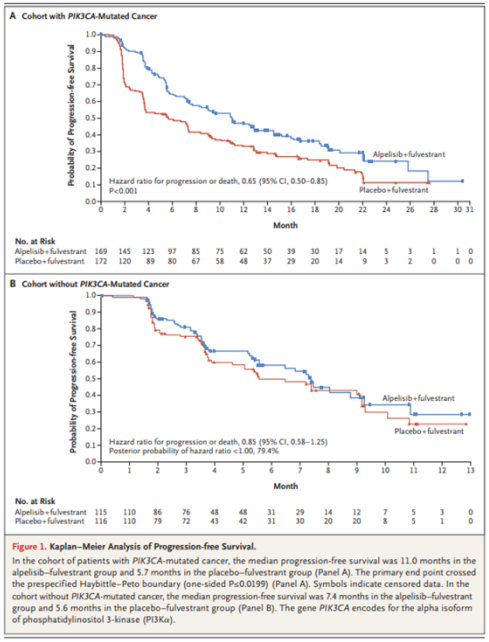
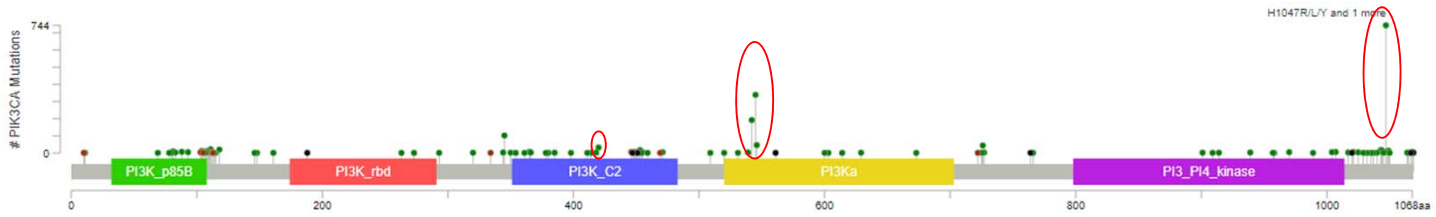
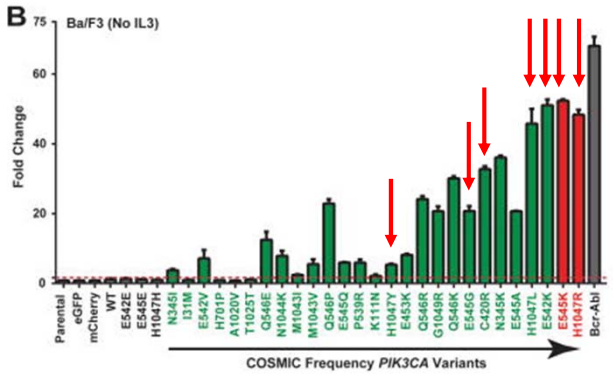


Figure 1. Kaplan–Meier Analysis of Progression-free Survival.
In the cohort of patients with *PIK3CA*-mutated cancer, the median progression-free survival was 11.0 months in the alpelisib–fulvestrant group and 5.7 months in the placebo–fulvestrant group (Panel A). The primary end point crossed the prespecified Haybittle–Peto boundary (one-sided P≤0.0199) (Panel A). Symbols indicate censored data. In the cohort without *PIK3CA*-mutated cancer, the median progression-free survival was 7.4 months in the alpelisib–fulvestrant group and 5.6 months in the placebo–fulvestrant group (Panel B). The gene *PIK3CA* encodes for the alpha isoform of phosphatidylinositol 3-kinase (PI3Kα).

Pitfalls and Landmines: Targeted CDX Assays



- The variants detected in the CDx assay are the only ones with proven association with therapy response
- But that doesn't mean others won't respond



Pitfalls and Landmines: Fusion Detection

- Fusion detection efficacy varies based on:
  - DNA vs RNA NGS
  - Sample type tested
- This is an important hole to fill – when appropriate!

DNA NGS (=driving):
- See lots of beautiful countryside
- Comparatively long, challenging

RNA NGS (=flying):
- More efficient
- But only if you have well timed layovers (= specimen quality)

Types of Results: A Different View

- Informative and actionable (on label)
- Informative and *maybe* actionable
- Informative but not actionable
- Not informative (stop)
- Not informative (keep pursuing)

Types of Results: A Different View

- Informative and actionable (on label)
- Informative and *maybe* actionable
- Informative but not actionable
- Not informative (stop)
- Not informative (keep pursuing)

- Will be listed in top tier for reporting
- Defined target in a defined tumor type with FDA approval for that indication
  - ** the test itself might not be FDA approved
  - ** opinion: that should not matter

Types of Results: A Different View

- Informative and actionable (on label)
- Informative and *maybe* actionable
- Informative but not actionable
- Not informative (stop)
- Not informative (keep pursuing)

- Tiering may be variable
- Typically this is a target that has FDA-approved therapy in a different indication
  - Example: *BRAF* p.V600E detected in an ovarian serous carcinoma
  - Rare!
  - What does this mean for therapy???
    - Response to BRAFi is tumor-type specific

Types of Results: A Different View

- Informative and actionable (on label)
- Informative and *maybe* actionable
- Informative but not actionable
- Not informative (stop)
- Not informative (keep pursuing)

- Tiering may be variable
- Typically this is a known driver event that is not associated with therapy
  - Example: *KRAS* p.G12V in NSCLC
  - Common finding
  - Is most likely the driver event for this tumor
    - Additional driver events are unlikely, even if undetected by testing platform
  - This might be something that could go into *maybe* actionable depending on clinical trial availability + patient PS + patient interest

Types of Results: A Different View

- Informative and actionable (on label)
- Informative and *maybe* actionable
- Informative but not actionable
- Not informative (stop)
- Not informative (keep pursuing)

- Many alterations may be in VUS section
- Typically lots of passenger mutations
- Example: No driver mutations identified in a squamous NSCLC, patient with poor PS, DNA-NGS performed
- OK to stop testing at this point
- (Also OK to pursue fusion by RNA-NGS, but low pre-test probability)

Types of Results: A Different View

- Informative and actionable (on label)
- Informative and *maybe* actionable
- Informative but not actionable
- Not informative (stop)
- Not informative (keep pursuing)

- This is about knowing the 'holes' in the assay(s)
- Is there a high pre-test probability for an actionable alteration?
- Example: DNA-NGS in never-smoker with adenocarcinoma is negative for driver alterations.
  - This is an example where RNA-NGS fusion testing is likely to be of highest yield

Look at the Methods Section!

- Was tumor enrichment applied?
- What technology was used for testing?
- What is the stated LOD?
- What types of alterations are detected?

Resources to Use

- NCCN Biomarker Compendium

- This is a rapid way to find a specific GL for a specific marker

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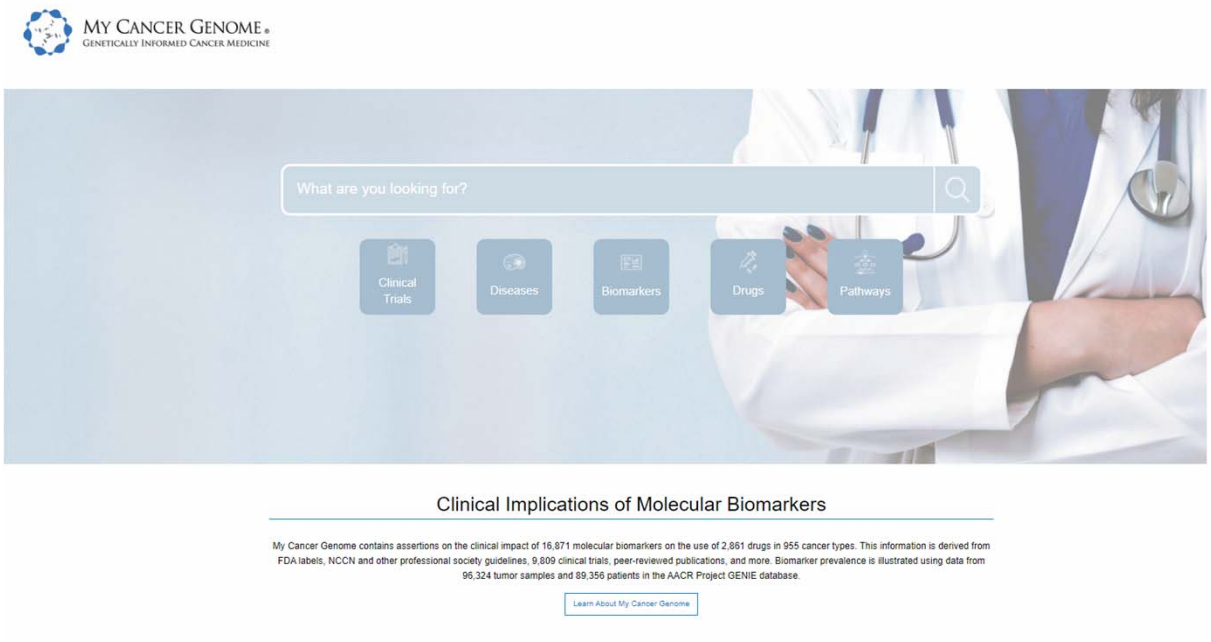
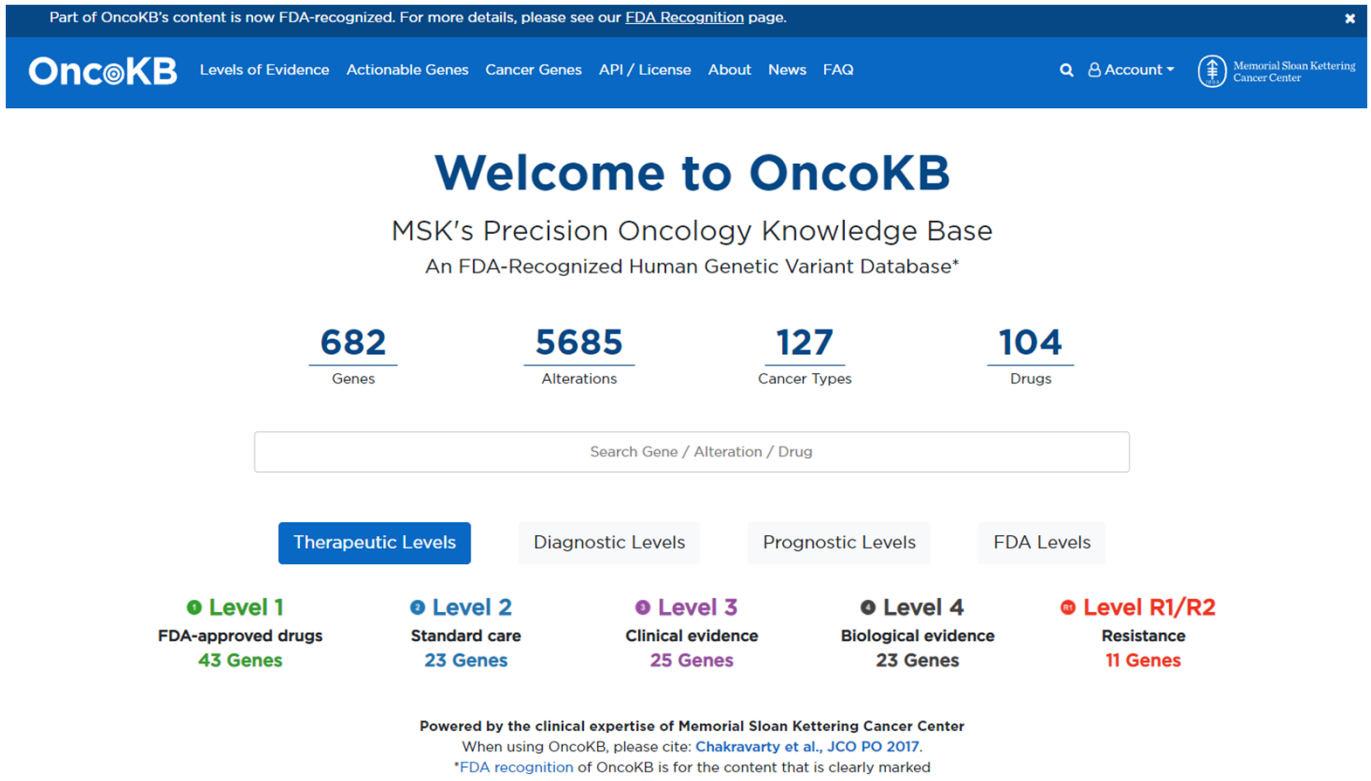
Resources to Use

- MyCancerGenome.org



Resources to Use

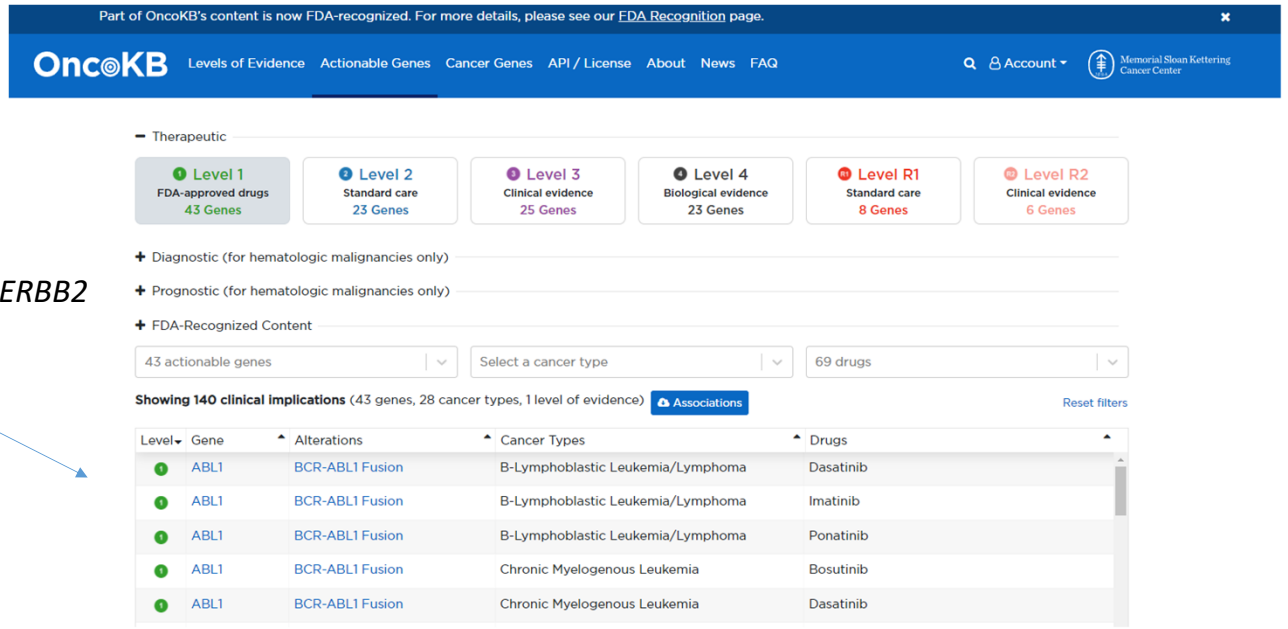
- OncoKB



OncoKB example

- NSCLC with *ERBB2* p.D769H

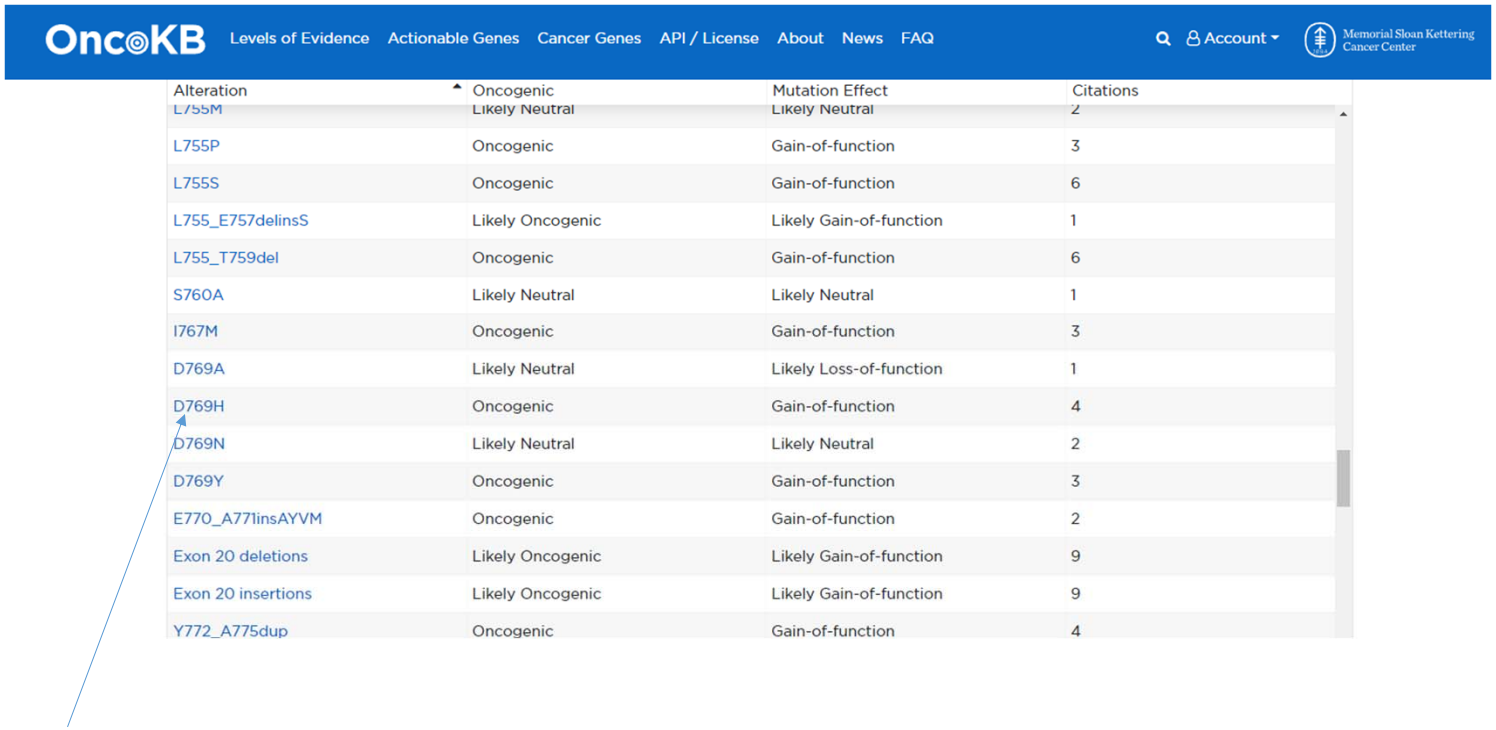
Navigate to *ERBB2*



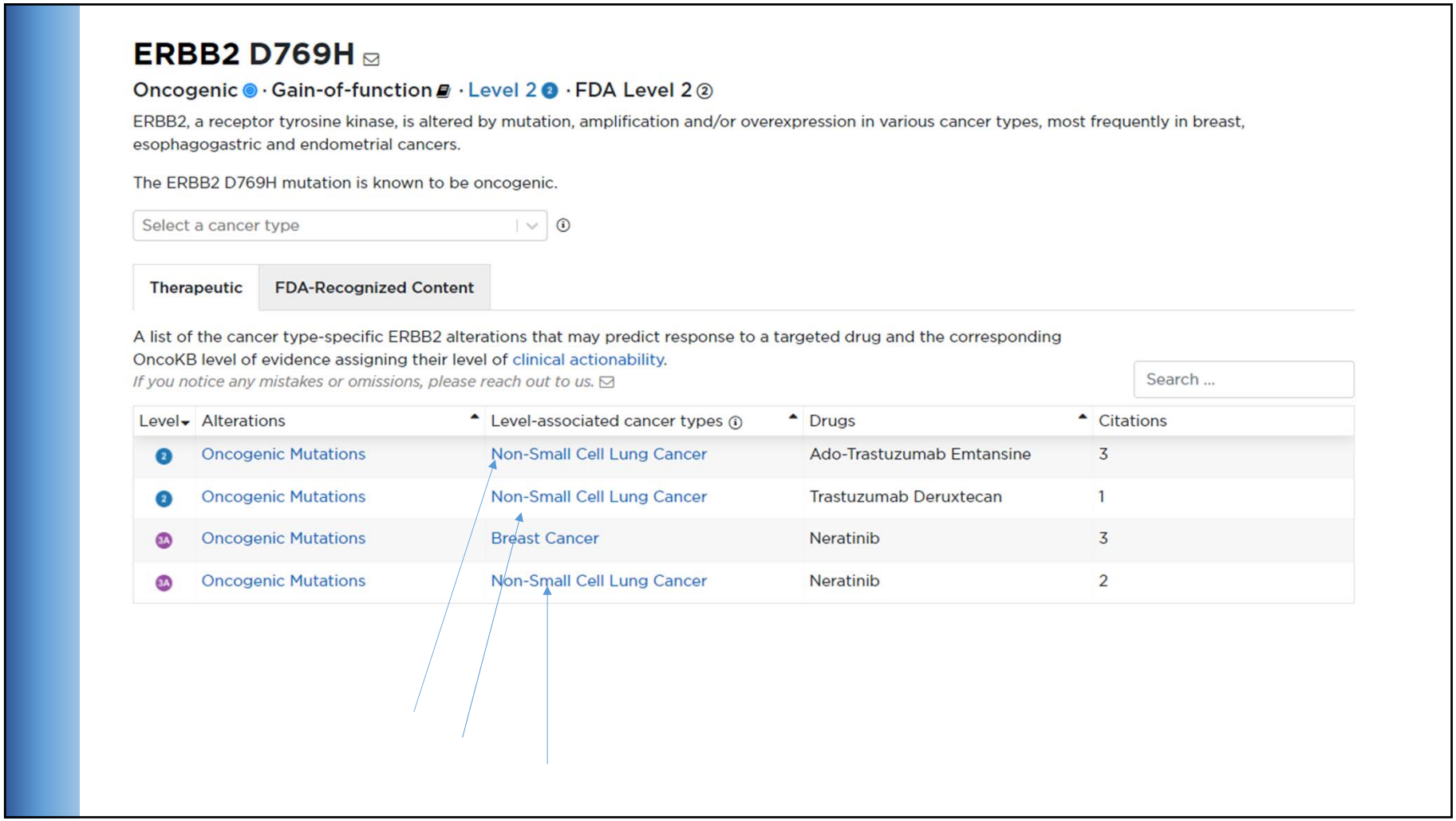
ERBB2	Amplification	Breast Cancer	Ado-Trastuzumab Emtansine
ERBB2	Amplification	Breast Cancer	Lapatinib + Capecitabine, Lapatinib + Letrozole
ERBB2	Amplification	Breast Cancer	Margetuximab + Chemotherapy
ERBB2	Amplification	Breast Cancer	Neratinib, Neratinib + Capecitabine
ERBB2	Amplification	Breast Cancer	Trastuzumab + Pertuzumab + Chemotherapy
ERBB2	Amplification	Breast Cancer	Trastuzumab + Tucatinib + Capecitabine
ERBB2	Amplification	Breast Cancer	Trastuzumab Deruxtecan
ERBB2	Amplification	Breast Cancer	Trastuzumab, Trastuzumab + Chemotherapy
ERBB2	Amplification	Esophagogastric Cancer	Pembrolizumab + Trastuzumab + Chemotherapy
ERBB2	Amplification	Esophagogastric Cancer	Trastuzumab + Chemotherapy
ERBB2	Amplification	Esophagogastric Cancer	Trastuzumab Deruxtecan

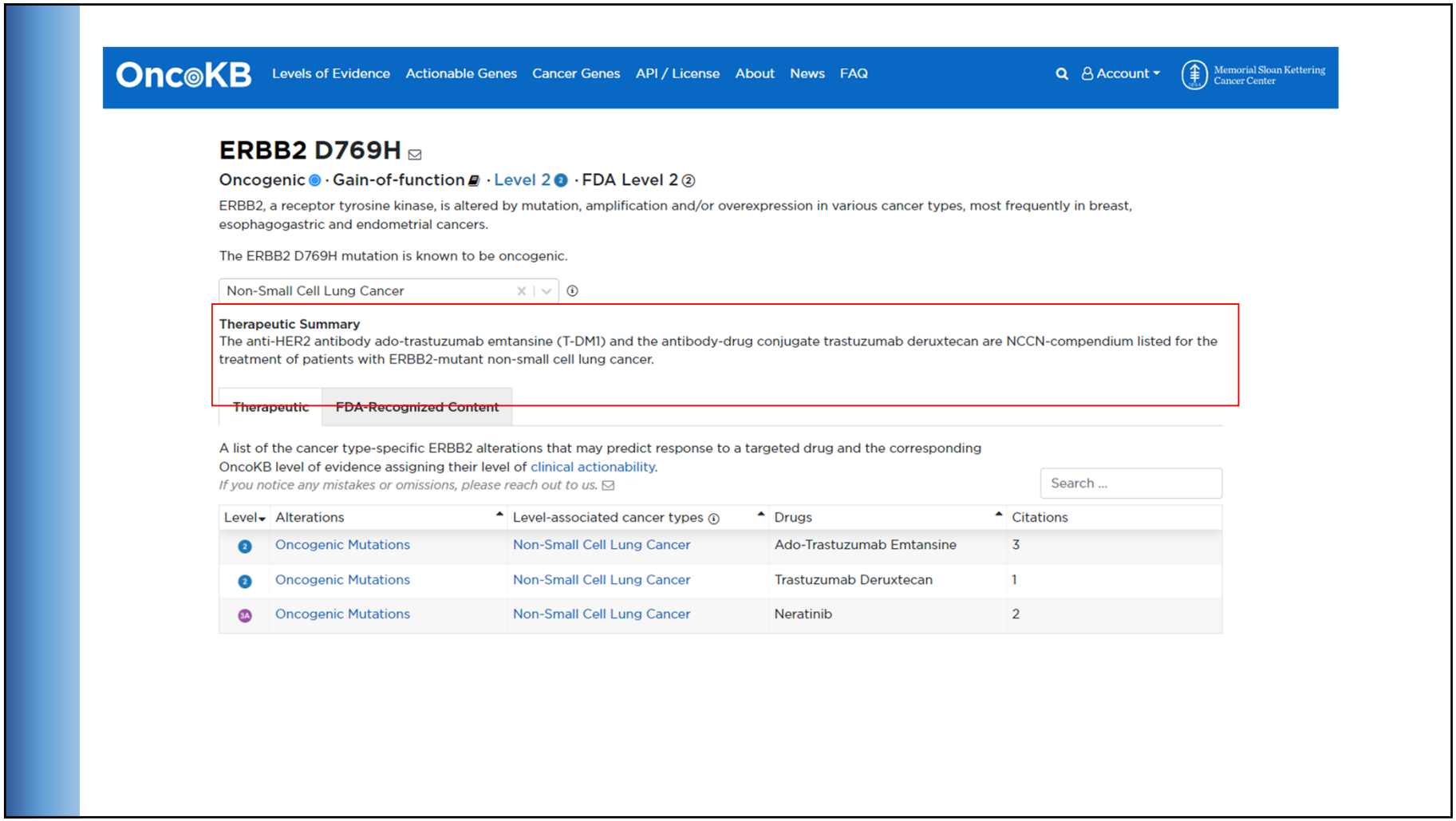
You can click on any of these…

This will take you to a more detailed list



Alteration	Oncogenic	Mutation Effect	Citations
L755M	Likely Neutral	Likely Neutral	2
L755P	Oncogenic	Gain-of-function	3
L755S	Oncogenic	Gain-of-function	6
L755_E757delinsS	Likely Oncogenic	Likely Gain-of-function	1
L755_T759del	Oncogenic	Gain-of-function	6
S760A	Likely Neutral	Likely Neutral	1
I767M	Oncogenic	Gain-of-function	3
D769A	Likely Neutral	Likely Loss-of-function	1
D769H	Oncogenic	Gain-of-function	4
D769N	Likely Neutral	Likely Neutral	2
D769Y	Oncogenic	Gain-of-function	3
E770_A771insAYVM	Oncogenic	Gain-of-function	2
Exon 20 deletions	Likely Oncogenic	Likely Gain-of-function	9
Exon 20 insertions	Likely Oncogenic	Likely Gain-of-function	9
Y772_A775dup	Oncogenic	Gain-of-function	4





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☐	Non-Small Cell Lung Cancer	ERBB2 (HER2) mutation	ERBB2	2B	Emerging biomarkers to identify novel therapies for patients with metastatic NSCLC Genetic alteration (ie, Driver event): ERBB2 (HER2) mutations	NSCL-H

National Comprehensive Cancer Network®

NCCN Guidelines Version 7.2021
Non-Small Cell Lung Cancer

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Discussion

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification	Crizotinib[1-2] Capmatinib[3]
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine[4] Fam-trastuzumab deruxtecan-nxki[5]

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Summary

- Know enough about the testing methodology to know what the 'holes' are
  - Use this to decide whether additional exploration is warranted given clinical considerations
- Learn the nuances of how results are reported by the lab(s) most frequently used for testing
- Sometimes, being able to dig for information on variants separately can be illuminating!

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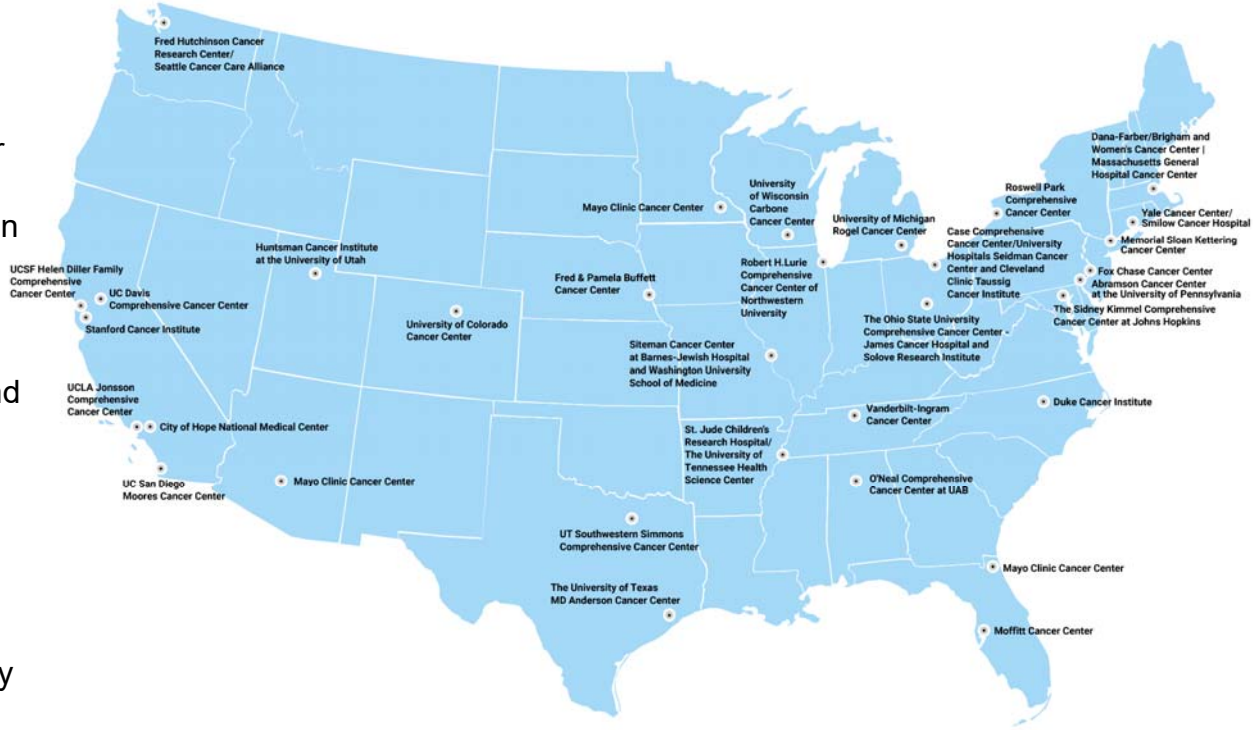
  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives
- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally



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