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

Overcoming Operational Challenges of Personalized Cancer Therapy

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SAFIR01

- 423 patients consented
  - Out of how many new metastatic patients ?
- 195 "targetable" mutations
  - 23 (5%) had standard of care altered outside trials
  - 13 (3%) had clinical benefit from their therapy…….
- Important research topic
  - Didn't change standard of care for 95% of patients
  - No evaluation of the psychological/QoL consequences of this unactionable extra knowledge

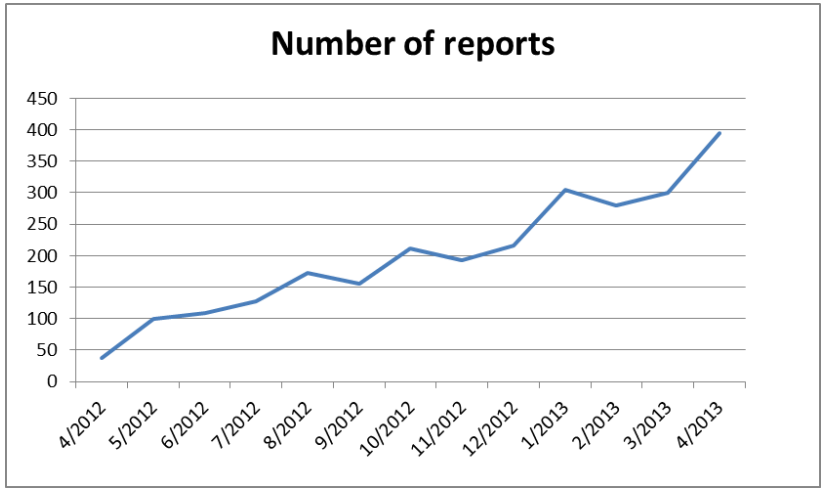
Andre et al……et Bonnefoi. *Lancet Oncol* 2014; 15: 267–74

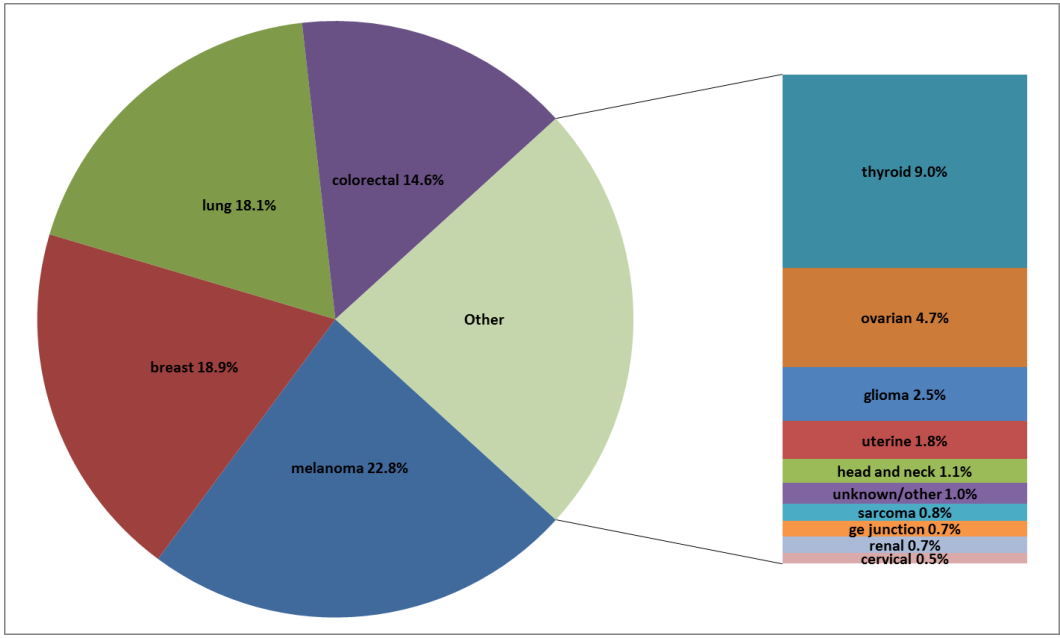
Clinical Testing: Real Clinical Utility or Irrational Exuberance?

- Multidisciplinary decision team
- Distinguish between clinical validity based on level of evidence and “actionable” interest based on hypothesis
  - Outside of a clinical trial
- Avoid or manage conflicts
  - Academic (research intent as clinical service)
  - Competition (between institutions or with industry)

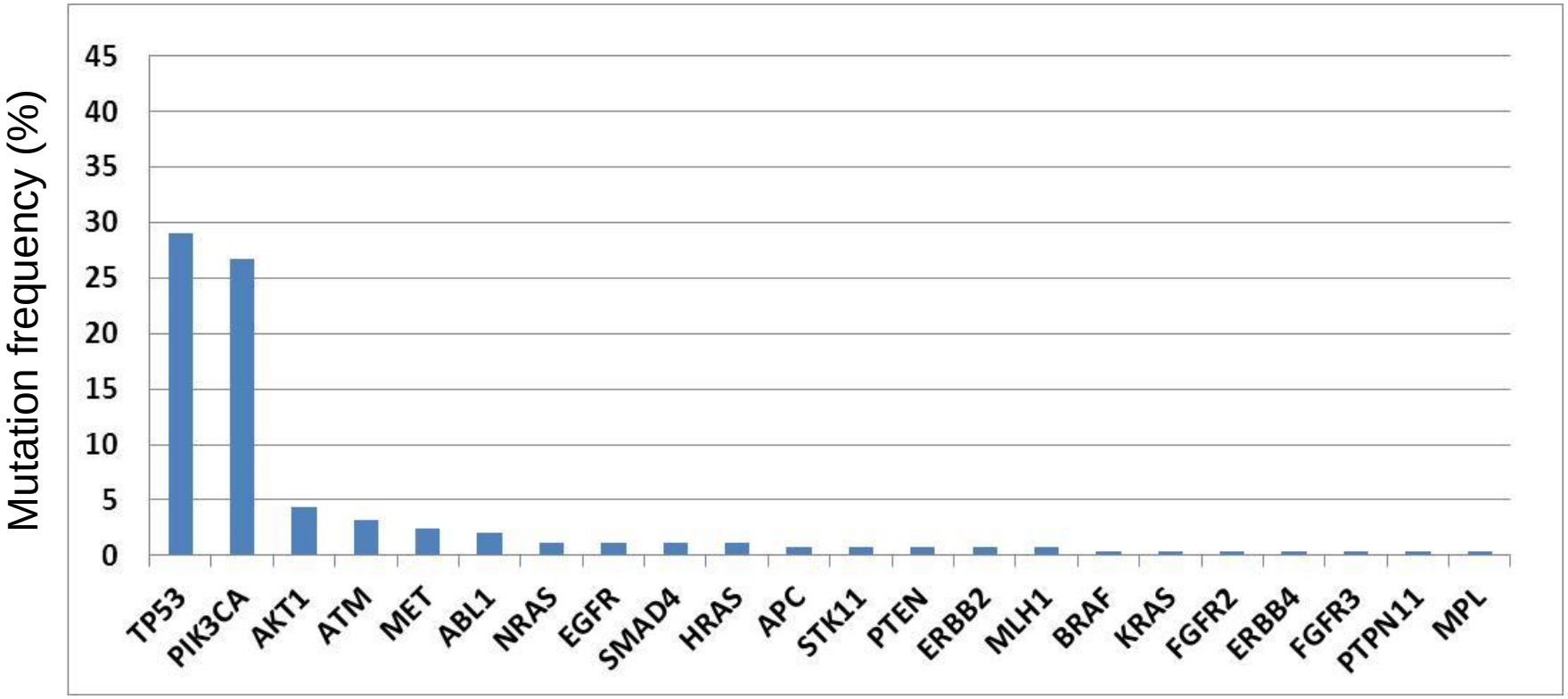
NGS Clinical Test Volume Grows Rapidly

- DNA sequencing with 46-gene panel
- 3354 CMS46 reports 2012-2013
- 3035 unique patients at MDACC





BREAST CANCER

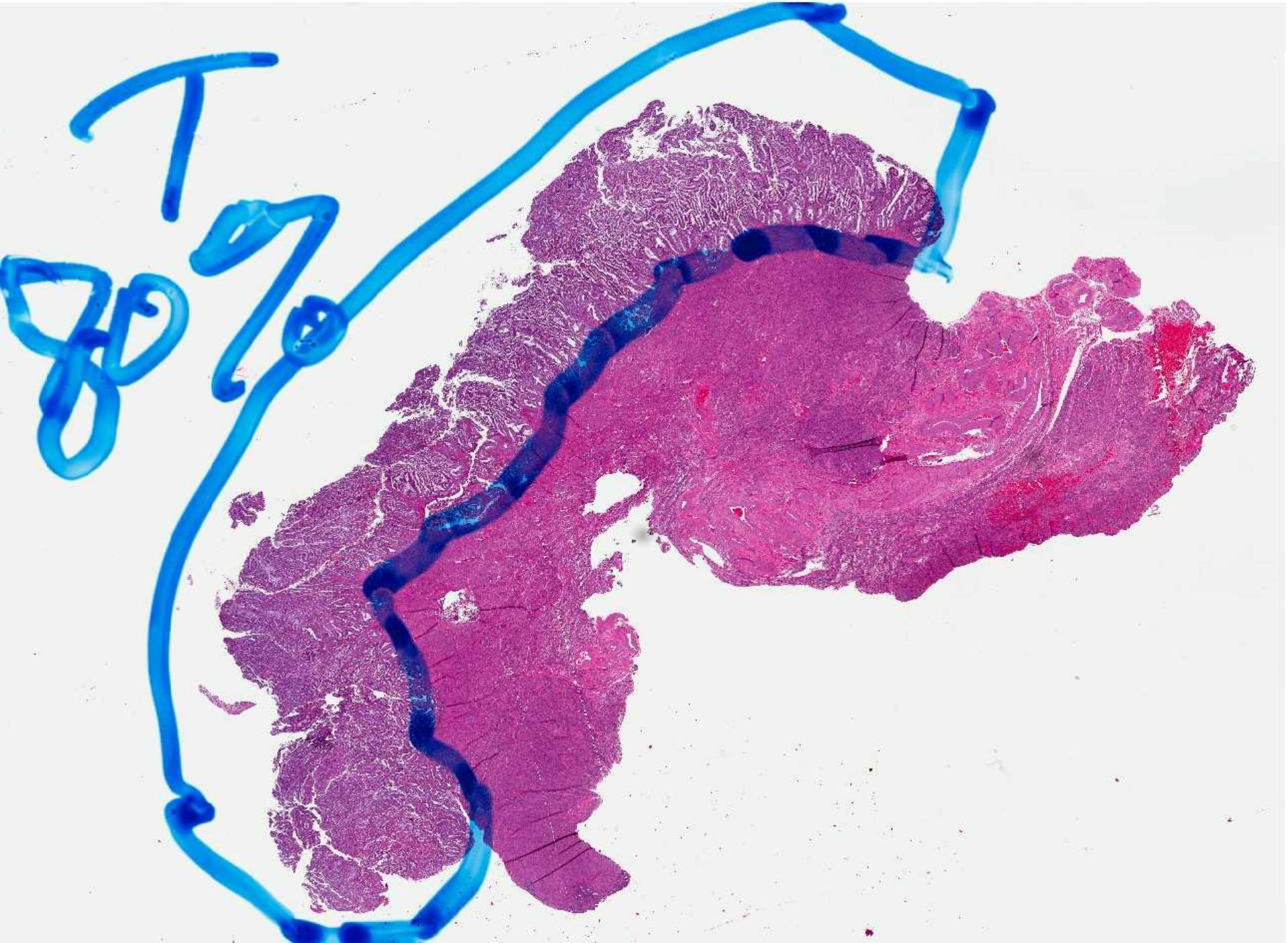


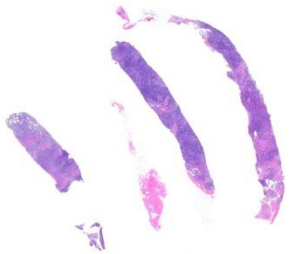
Clinical NGS requires high coverage depth

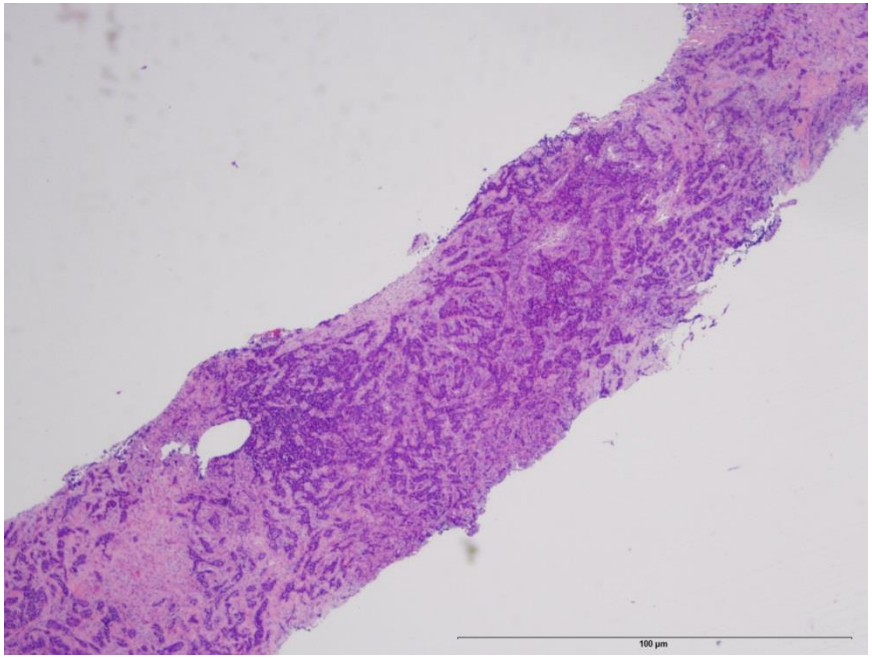
- the trade-off in generating so many parallel sequences using PCR /DNA polymerase is loss of accuracy.
- NGS platforms have approximately 10-fold higher error rates (1 in 1000 bases) versus Sanger sequencing (1 in 10,000 bases).
- For clinical accuracy, each template requires 100’s of sequence reads to account for sequencing errors, non-neoplastic DNA “contamination”, and artifacts from formalin.

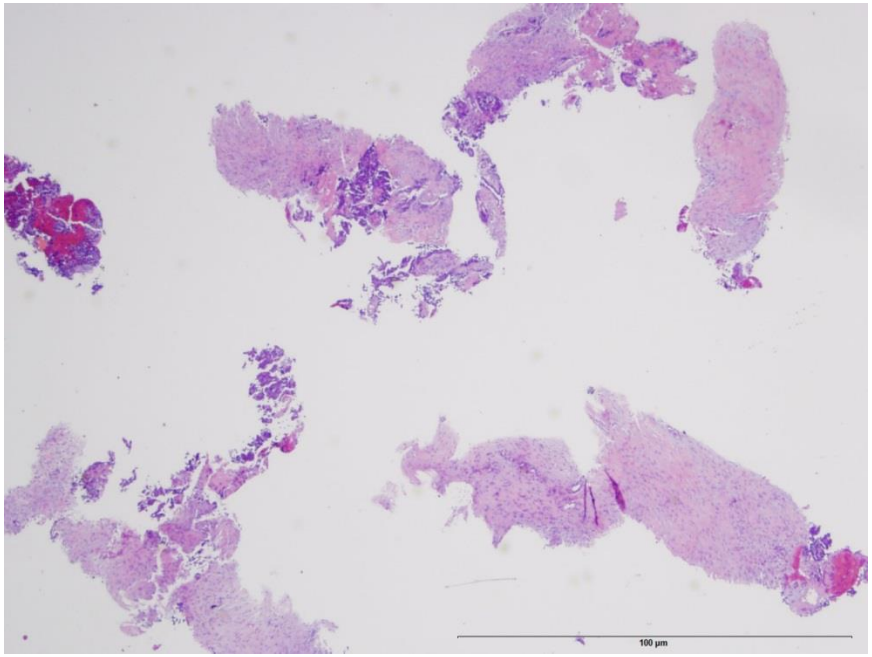
CLIA next-gen sequencing of solid tumors

- High coverage: multiple (~500x) reads of the same sequence to gain confidence in result
  - Critical when ratio of neoplastic to non-neoplastic cells is low
  - Allows signal to be sifted from the noise
- Examination of reads in both directions to rule out artifacts
- Confirm or rule out sequence variant using an additional method (e.g. Sanger)



Omental biopsy	Breast biopsy
	





Not all biopsies are equal!

Adequacy for histologic diagnosis vs. adequacy for biomarker testing

- Very difficult issue
- Not unusual to make a diagnosis of cancer from only a few cells
- These same cases might be unsuitable for molecular testing
- Focus on tissue qualification in Pathology
- Engage the interventional radiologists and the cytologists

What about an FNA sample?

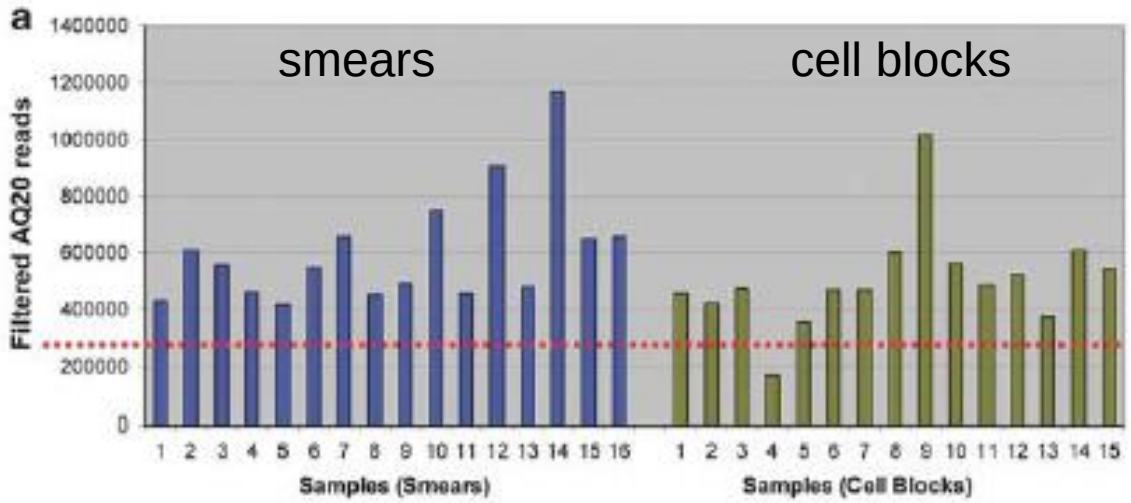
MODERN PATHOLOGY (2013), 1–14

Methods in Pathology

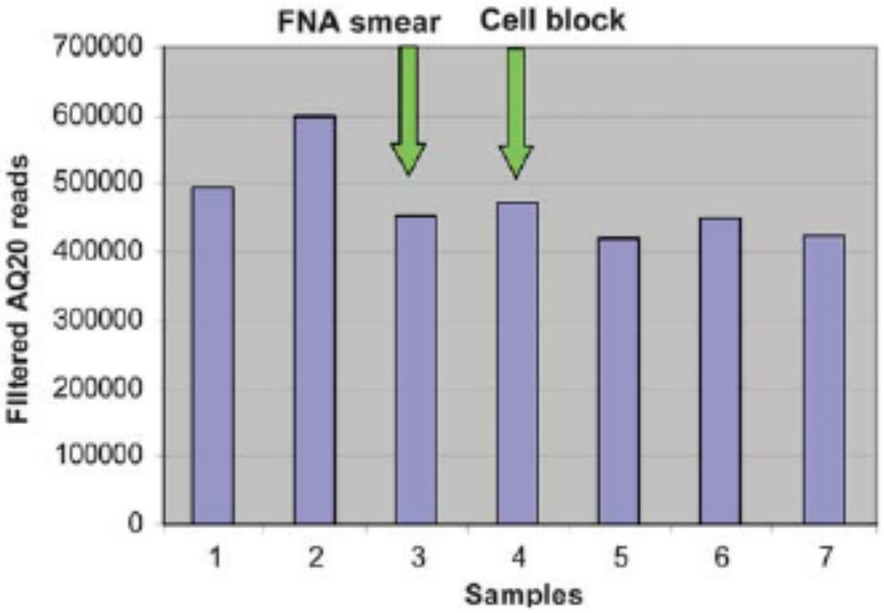
Next-generation sequencing-based multi-gene mutation profiling of solid tumors using fine needle aspiration samples: promises and challenges for routine clinical diagnostics

Rashmi Kanagal-Shamanna, Bryce P Portier, Rajesh R Singh, Mark J Routbort, Kenneth D Aldape, Brian A Handal, Hamed Rahimi, Neelima G Reddy, Bedia A Barkoh, Bal M Mishra, Abhaya V Paladugu, Jawad H Manekia, Neda Kalhor, Sinchita Roy Chowdhuri, Gregg A Staerkel, L Jeffrey Medeiros, Rajyalakshmi Luthra and Keyur P Patel

FNA Direct Smears or Cell Block Sections (FFPE) Are Equivalent To Excised Tumor Tissue (FFPE) For Next-Gen DNASeq In The Clinical Lab



FNA samples from different NGS runs



<u>A single NGS run</u>

1 FNA smear

1 FNA cell block

5 excised tumors

Kanagal-Shamanna *et al*. Mod Pathol;2013;27:314-27

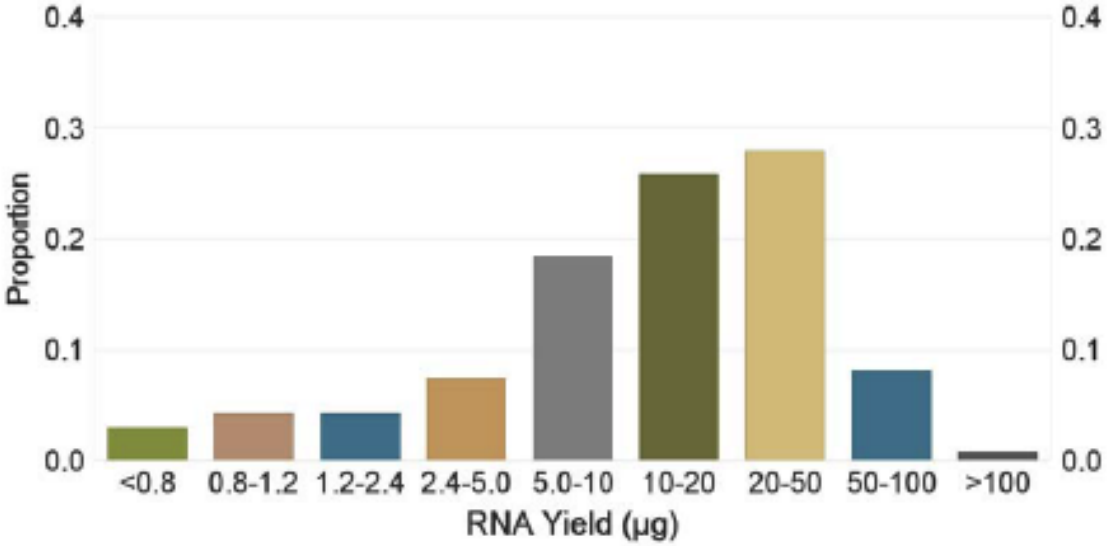
What about Nucleic Acid Preservatives?

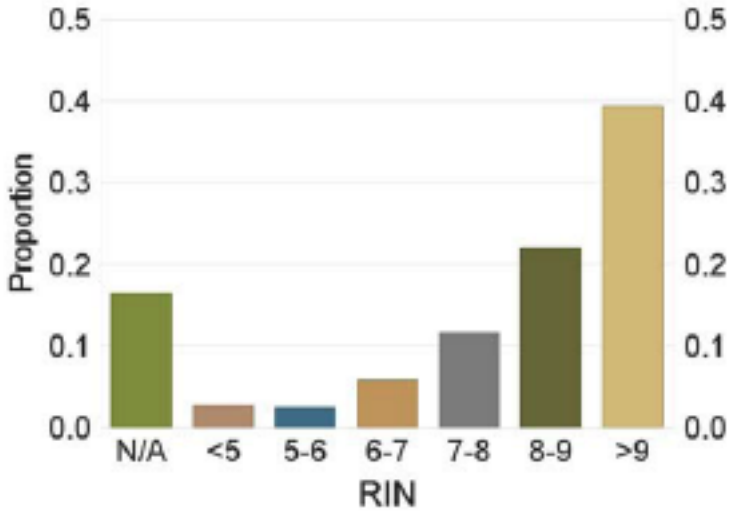
Prospective registry trial at MDACC (PI: Stacy Moulder).

Samples collected at time of clinical procedure following a SOP

Pass rates represent Dx, & yield & quality of RNA & gene expression microarray data

Sample Type	ER+/HER2-			TNBC		
	Pass	Fail	Rate	Pass	Fail	Rate
FNA	39	7	85%	24	5	83%
CBX	104	0	100%	39	2	95%
Surgical	74	5	94%	14	0	100%





Clinical Testing For Personalized Cancer Therapy

1. Requires a truly multidisciplinary decision and active participation
2. Seek clinical validity and clinical utility before implementation as standard of care
    - Otherwise, it is reasonable to perform within a clinical trial
3. Only perform in an accredited diagnostic laboratory
    - Procedures and requirements are different from research
4. Quality of the sample is critical to success
    - Ideally collect samples with the best quality molecules
    - Otherwise, sample qualification is essential
        - Need to demonstrate feasibility with limited samples