Comparison of molecular oncology **laboratory-developed tests (LDTs)** and **FDA-approved assays**

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- Laboratory-developed tests (LDTs) are created within a clinical laboratory and validated to ensure quality, safety, accuracy
- Often address “orphan” diseases or conditions for which no other test is available
- Allow implementation of new medical knowledge
- FDA-approved assays are kits that go through a costly, burdensome process similar to medical devices

Bottom line up front

- Performance is excellent for *both* LDTs and FDA approved tests
- Both types of tests have strengths and weaknesses
- Most laboratories using FDA approved assays reported modifying the approved procedure, rendering it an LDT

Background: Debate about the regulation of molecular assays has focused on analytical performance

- One frequent assumption is that FDA approved assays have superior performance compared to LDTs

- Are there any studies that directly compare performance?

The College of American Pathologists surveyed hundreds of laboratories (academic, non-academic, commercial, U.S., non-U.S.)

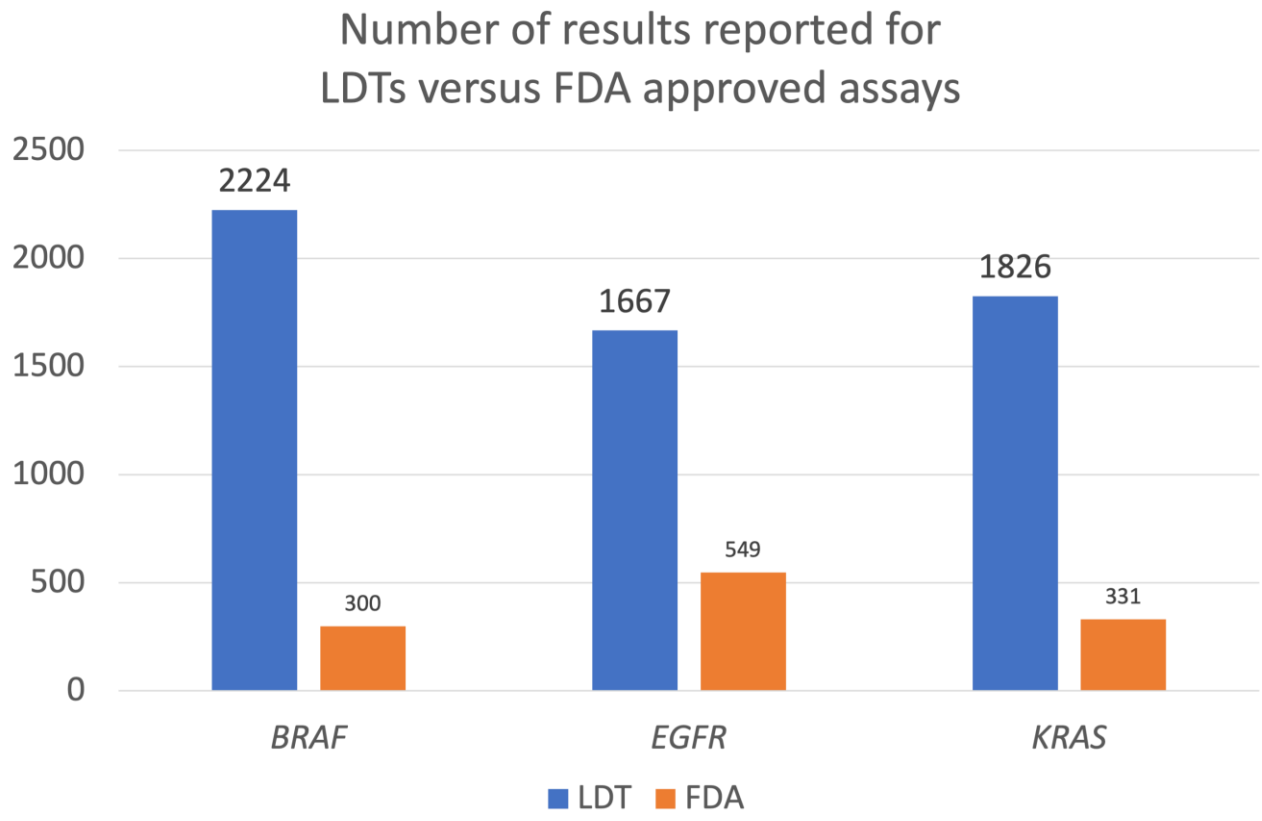
- *BRAF* – 212 unique laboratories
  - 14 samples, 8 mailings, 2524 total responses (2404 responses with methodological details)
  - Variants: Wild type, p.V600E, p.V600K

- *EGFR* – 197 unique laboratories
  - 11 samples, 5 mailings, 2216 total responses (2176 responses with methodological details)
  - Variants: Wild type, exon 19 del, p.G719A, p.L858R, p.L861Q, p.T790M

- *KRAS* – 282 unique laboratories
  - 10 samples, 4 mailings, 2157 total responses (2112 responses with methodological details)
  - Variants: Wild type, p.G12A, p.G12C, p.G12R, p.G12S, p.G12V, p.G13D

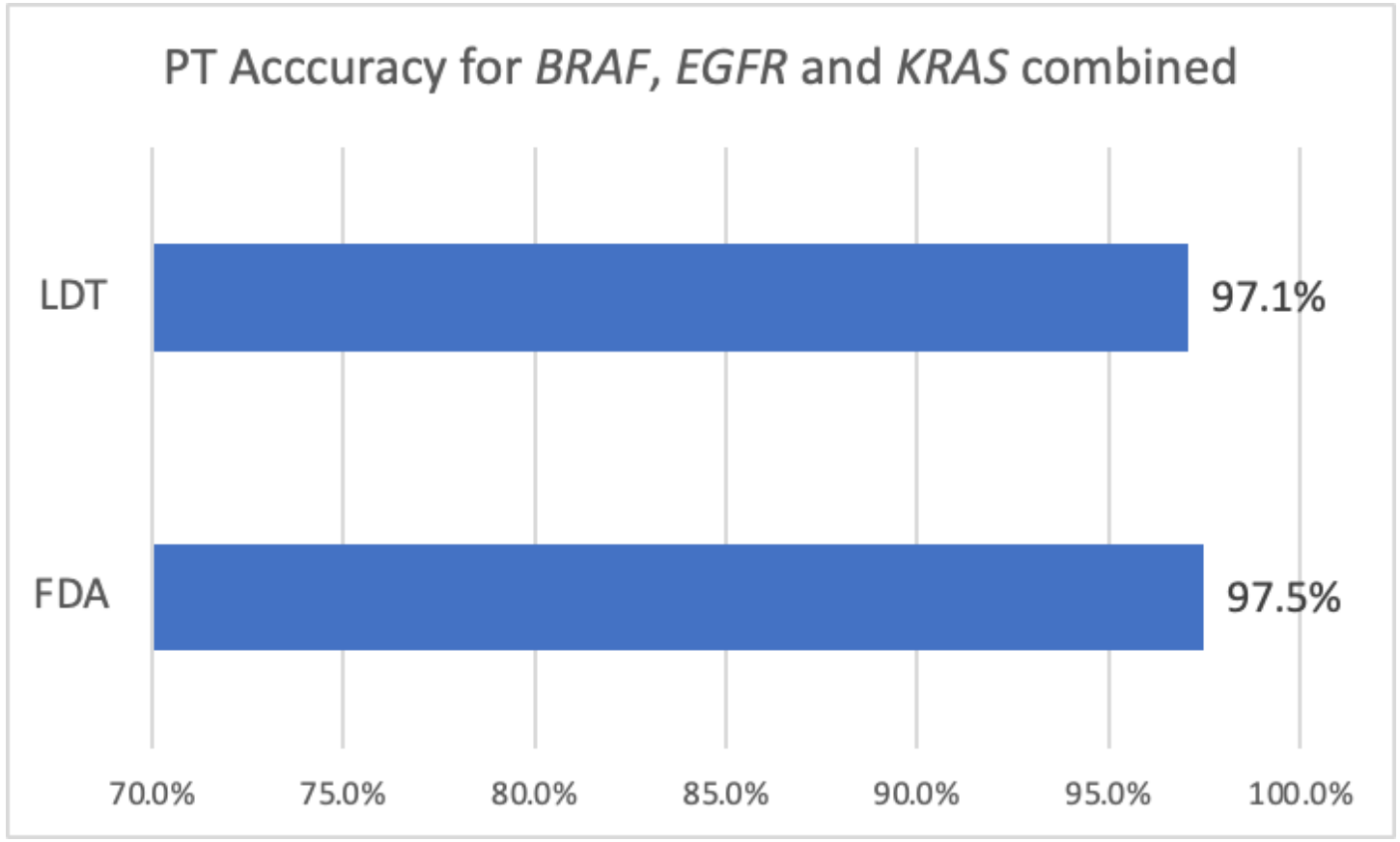
Kim AS, *JAMA Oncol* 2018

More participant laboratories reported results for LDTs than FDA approved assays



Kim AS, *JAMA Oncol* 2018

Both LDTs and FDA approved assays exceeded 97% accuracy for three common genes



Kim AS, *JAMA Oncol* 2018

There were some differences in performance between LDTs and FDA-approved assays, but no systematic pattern

Acceptable results for LDTs and FDA approved assays				
	LDT, % (No.)	**FDA, % (No.)**	**X^2 test**	***P* value**
BRAF	96.6% (2224)	93.0% (300)	9.1800	.002
EGFR	97.6% (1667)	99.1% (549)	4.6011	.03
KRAS	97.4% (1826)	98.8% (331)	-	.16

Kim AS, *JAMA Oncol* 2018

BRAF: Performance differences between LDTs and FDA-approved assays were related to one specific, rare variant

- *BRAF* p.V600K predicts a favorable response to BRAF inhibitors for some tumors like melanoma
- Accuracy: LDTs 88.0%; FDA 66.1%; *P*<.001
- The most commonly used FDA-approved assay is not designed to detect this clinically significant *BRAF* variant

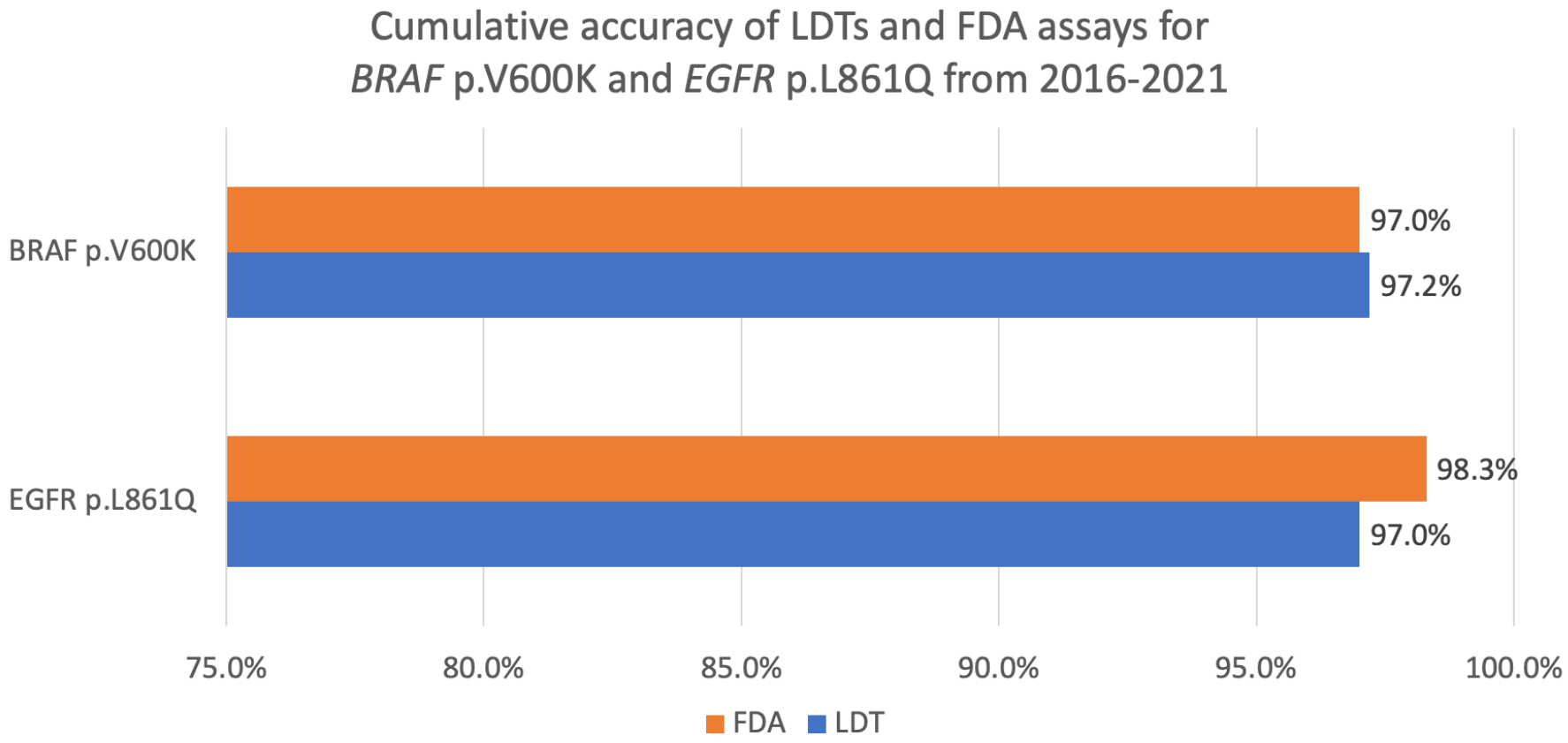
Kim AS, *JAMA Oncol* 2018

EGFR: Performance differences between LDTs and FDA-approved assays were related to one specific variant

- *EGFR* p.L861Q comprises 2% percent of *EGFR* mutations in lung adenocarcinomas
- Associated with low efficacy or complete resistance to some cancer medications (EGFR inhibitors)
- Accuracy: LDT 90.7%; FDA 100%; *P*=.04

Kim AS, *JAMA Oncol* 2018

Since 2015, both LDTs and FDA-approved assays have exhibited ≥ 97% accuracy for these rare variants



Molecular Oncology Committee, unpublished data

More than 60% of laboratories using FDA-approved assays modified the approved protocol, rendering it an LDT

- Modifications included the validation of new specimen types (e.g., fine needle aspiration specimens) and changes to the FDA-approved lower limit of detection of the assay

Kim AS, *JAMA Oncol* 2018

Conclusions

- Performance is excellent for *both* LDTs and FDA approved tests for *BRAF, EGFR*, and *KRAS*
- Both types of tests exhibit strengths and weaknesses that can help laboratories with assay selection and validation
- Majority of laboratories using FDA approved assays reported modifying the approved procedure, rendering it an LDT