Update On The Adoption And Utilization Of Emerging Precision Medicine Biomarkers And Technologies In Routine Clinical Care

Companion Diagnostics Forum 2020 – October 28

Disclaimer

Some of the companies listed in this document may be DeciBio Consulting Clients or Customers; However, this project is entirely self funded by DeciBio Consulting

DeciBio Consulting, LLC
10203 Santa Monica Blvd., Ste. 400
Los Angeles, CA 90067
Phone: (310) 451-4510
Email: info@decibio.com
www.decibio.com

DeciBio Contacts:
Andrew Aijian: aijian@decibio.com

The precision oncology landscape continues to evolve at a rapid pace; in the past 2 years, multiple clinical, technological, commercial, and regulatory developments have impacted cancer care

Select Key Precision Medicine Developments; 2018 – 2020 YTD

- **03/16/2018** CMS finalizes **LCD for NGS** testing in advanced cancer patients

- **01/07/2019** Guardant launches its LUNAR-1 **MRD** assay to biopharma and academic researchers

- **03/07/2019** Paige.AI receives FDA breakthrough device designation for its AI-based **dig. path** tools

- **05/2020** Lilly's Retevmo and NVS' Tabrecta approved for RET fusion and METex14 skipping NSCLC, respectively

- **06/16/2020** FDA approves Keytruda in advanced patients with **TMB-H tumors, with F1CDx** as a CDx

- **07/30/2020** Tagrisso granted Breakthrough Designation for adjuvant treatment of pts. with stage IB-IIIA EGFR-mut. NSCLC

- **10/13/2020** Caris launches its CODEai **real-world data clinico-genomic database** with >215,000 patients

2018 2019 2020

- **03/30/2018** Foundation Medicine announces commercial availability of FoundationOne CDx, the first FDA-approved **CGP** assay

- **07/12/2018** Guardant announces Medicare coverage of Guardant360 assay in NSCLC under Palmetto GBA, coverage later expanded to all solid tumors

- **12/19 – 01/20** ArcherDx announces development of personalized **MRD** assay; receives breakthrough device designation

- **04/01/2020** FDA approves Sectra's and Leica's **digital pathology** solution for primary diagnosis

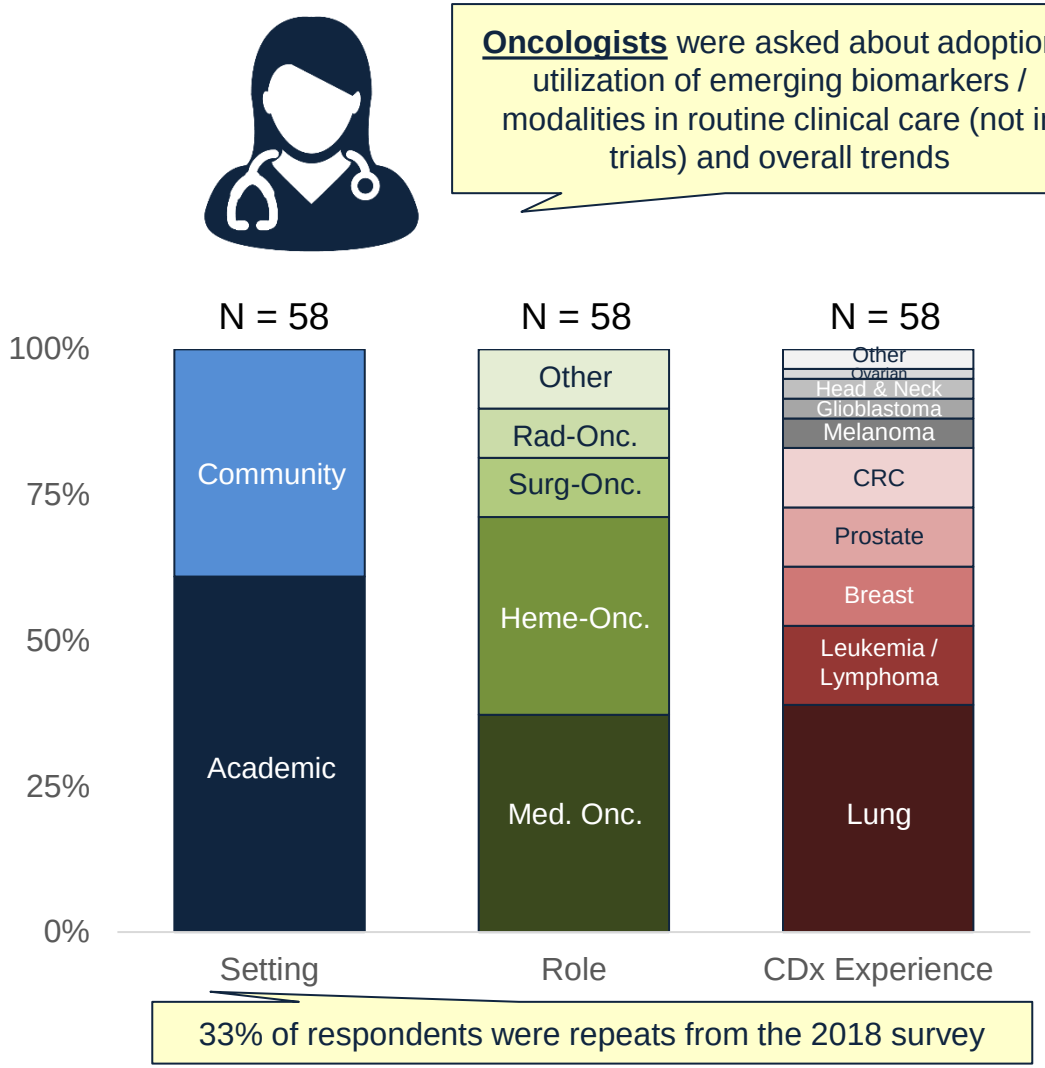
- **04/21/2020** FDA expanded authorization for use of **digital pathology** during the COVID-19 pandemic

- **07/2020** Guardant's Guardant360, then FMI's F1Liquid CDx become the first FDA-approved **liquid biopsy CDx** tests

- **09/2020** CMS grants LCD for Natera's Signatera for CRC **MRD** and a draft LCD for immunotherapy monitoring

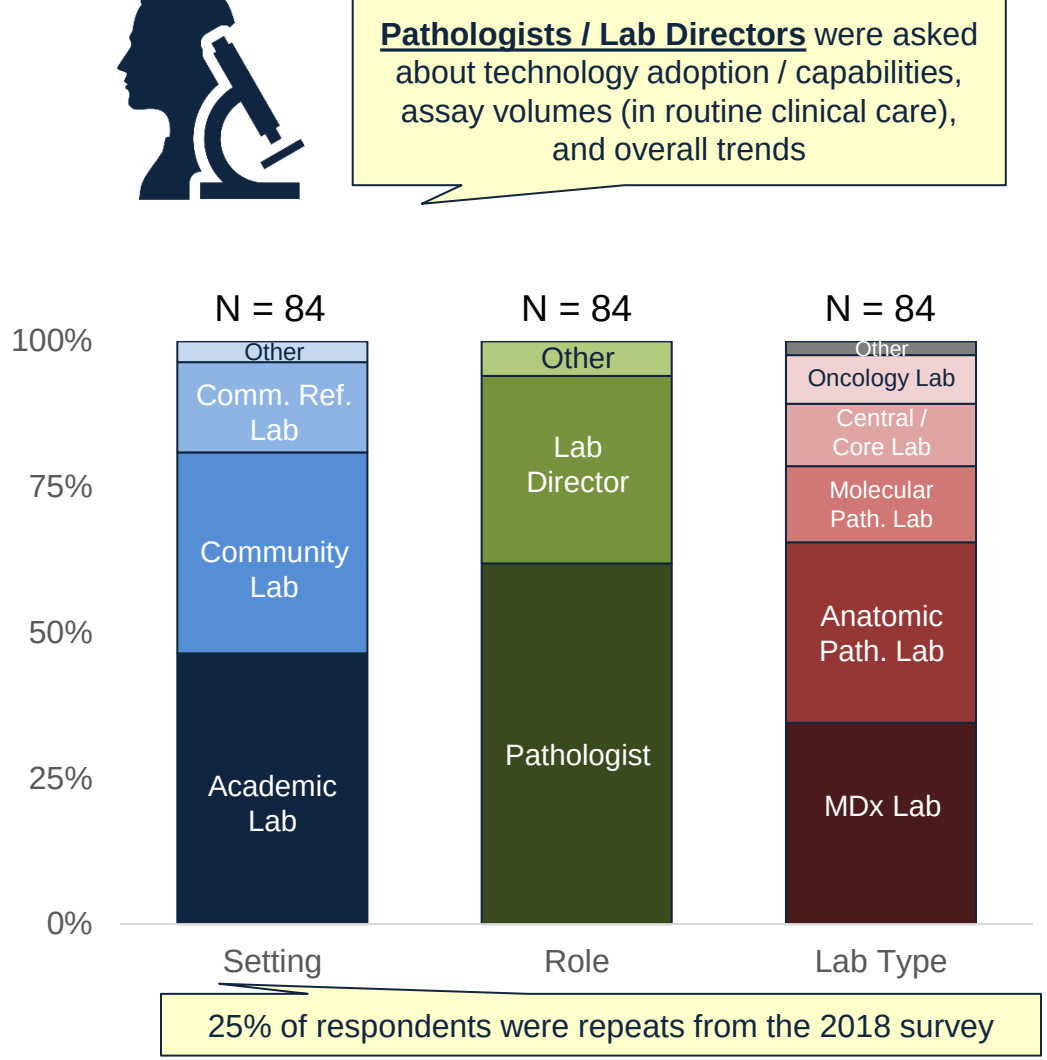
To evaluate how emerging / next-gen Dx tools are being integrated into routine cancer care, we conducted a pulse survey of >140 oncology stakeholders as a follow-up to a 2018 survey on this topic

Oncologists were asked about adoption / utilization of emerging biomarkers / modalities in routine clinical care (not in trials) and overall trends



33% of respondents were repeats from the 2018 survey

Pathologists / Lab Directors were asked about technology adoption / capabilities, assay volumes (in routine clinical care), and overall trends



25% of respondents were repeats from the 2018 survey

Source: DeciBio Dexter Expert Network

This analysis indicated significant changes and trends in precision medicine adoption, practices, and capabilities in just the past two years; five key themes emerged from the data and analysis

Key Takeaways

1. Adoption of biomarker testing has increased significantly, though stakeholders largely feel comfortable with the surge
2. NGS is becoming the standard method for molecular testing across cancer types; though broad decentralization of NGS (and especially other emerging biomarkers and modalities) is not expected in the foreseeable future
3. Confidence and adoption in liquid biopsies (LBx) is increasing; LBx is expected to be the most significant driving force of change in pathology / biomarker testing
4. Digital pathology (DP) use is growing, but the full clinical and workflow value propositions are yet to be realized; expectations for the value of DP remain high with increasing development and use of artificial intelligence
5. The role of the pathologist is changing, and pathologists of the future will need an entirely new skillset than today's pathologists

Adoption of precision medicine is increasing rapidly in routine clinical care, though stakeholders largely feel comfortable with their ability to accommodate this growth (for now)

The precision medicine load on oncologists and pathologists / labs is growing in mid-high double digits annually, both in patient volumes and number of markers…

Changes in adoption / utilization from 2018 - 2020

Oncologists

Average Number of Adv. Cancer patients: ▲ **~40%** (50 → 70)

Number of Different Biomarkers Ordered: ▲ **~25%** (7.5 → 9.5)

Share of Patients Tested: ▲ **~7%** (56% → 60%)

Pathologists

Biomarker Lab Tests Offered per Lab ▲ **~15%** (13 → 15+)

Biomarker Testing Volume ▲ **>110%**

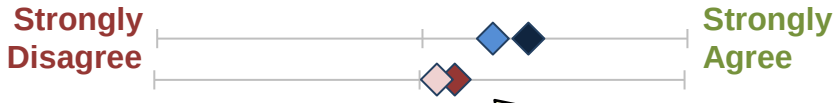
…However, oncologists and pathologists / lab directors seem to be managing the surge moderately effectively, generally showing slightly higher familiarity, knowledge, and ease of integration since 2018

Respondent agreement / disagreement with the following statements

I feel adequately informed about the current CDx testing guidelines

I am familiar with all of the companion diagnostic assay options available

It is easy for me to implement testing for a new biomarker into my care protocol / lab



Oncologists: ◇ 2018 ◆ 2020
Paths / LDs: ◇ 2018 ◆ 2020

There is room for improving new assay / technology implementation in labs

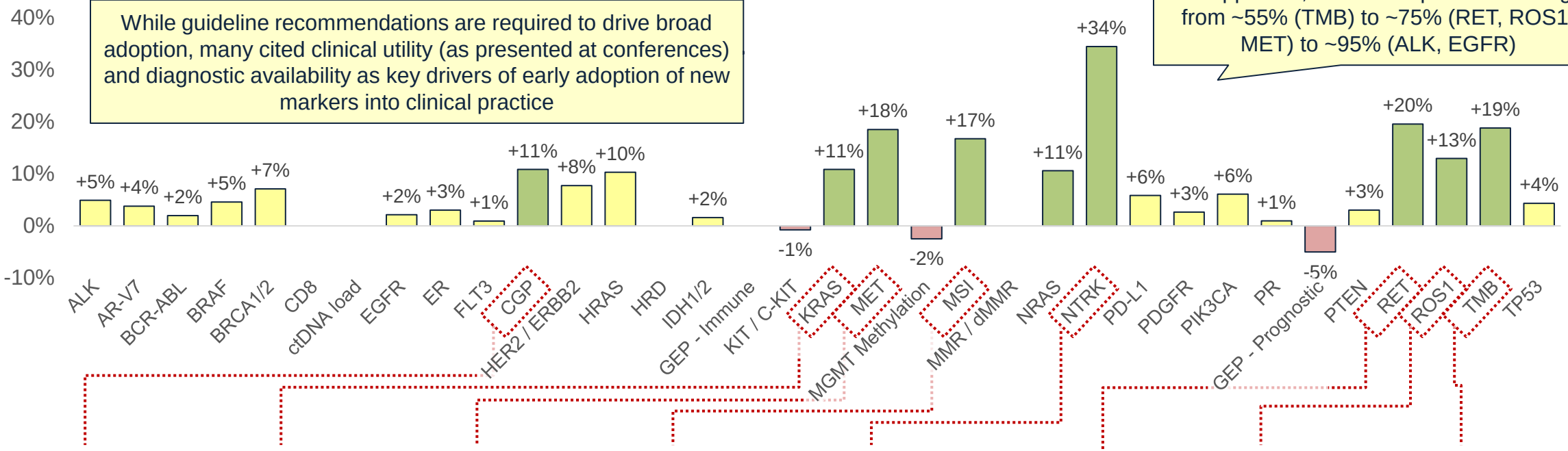
Much of the increase in precision medicine adoption is driven by recent drug / CDx approvals, demonstrating relatively rapid uptake of new markers and the expanding precision medicine arsenal

Changes in Biomarker Adoption Rates (Absolute Difference From 2018 to 2020)

Share of Oncologists

While guideline recommendations are required to drive broad adoption, many cited clinical utility (as presented at conferences) and diagnostic availability as key drivers of early adoption of new markers into clinical practice

In NSCLC, where many of the new markers are approved, overall adoption rates range from ~55% (TMB) to ~75% (RET, ROS1, MET) to ~95% (ALK, EGFR)



CMS — Final LCD covering CGP issued (**Mar 2018**)

AMGEN / GUARDANT HEALTH / QIAGEN — AMG510 Fast-Tracked for KRAS G12C+ NSCLC (**Sep 2019**)

TABRECTA / FOUNDATION MEDICINE — METex14 skipping mNSCLC (**May 2020**)

KEYTRUDA — Last-line MSI-H tumors (**May 2017**); 1L MSI-H mCRC (**Jul 2018**)

OPDIVO (nivolumab) + YERVOY (ipilimumab) — 2L MSI-H mCRC (**Jul 2018**)

VITRAKVI — Last-line NTRK Fusion+ tumors (**Nov 2018**)

ROZLYTREK — Last-line NTRK Fusion+ tumors (**Aug 2019**)

Retevmo (selpercatinib) / ThermoFisher SCIENTIFIC — RET Fusion+ lung and thyroid (**May 2020**)

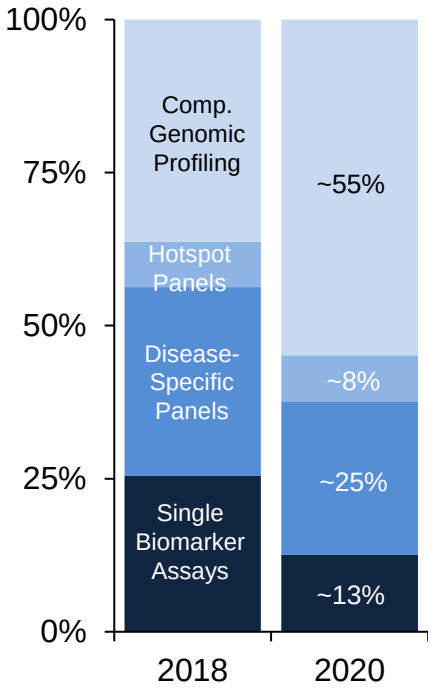
ROZLYTREK / FOUNDATION MEDICINE — ROS1+ mNSCLC (**Aug 2019**)

KEYTRUDA / FOUNDATION MEDICINE — Pan-tumor, last-line, TMB-H (**Jun 2020**)

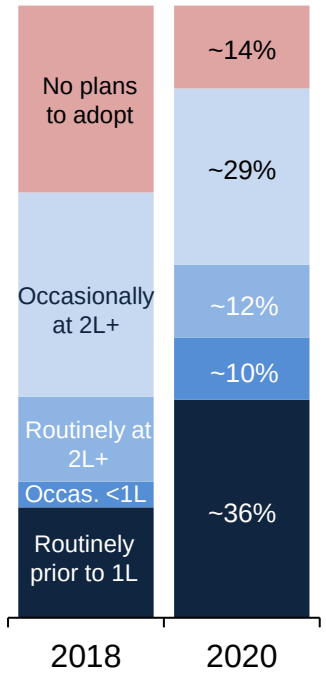
A key consequence of the penetration of precision medicine is the shift in genetic testing from single-marker methods (e.g., FISH, PCR) to panels (e.g., NGS), and the moderate centralization of testing

Oncologists estimate that genomic profiling now represents >50% of their genetic biomarker testing volumes, driven in part by tumor-agnostic markers

Estimated Share of Genetic Biomarker Testing by Method



Testing Approach for Tumor-Agnostic Biomarkers



Projections of future NGS decentralization remain unchanged, with respondents anticipating that the majority of clinical NGS testing will be conducted at advanced AMC labs, major cancer centers, and reference labs

Expected Degree of NGS Decentralization Among Lab Stakeholders

NGS testing will be distributed across **all hospitals / sites that evaluate cancer patients**

NGS testing will be widely distributed across **all AMCs** as well as reference labs

Major cancer centers and reference labs will conduct the vast majority of NGS testing

Reference labs will conduct an outsized majority of NGS testing

While NGS is widespread (**~65% of labs surveyed have an NGS platform** in house, and ~90% of all molecular path. labs); the expertise and costs required to deploy NGS for routine CDx testing in-house is still limiting (**only 40-60% of NGS adopters consider themselves capable of implementing tissue-based NGS CDx testing** in their lab in the near term)

*"…The expansion of molecular targets and genomic understanding of carcinogenesis is redefining precision medicine to the extent that **protein/gene analysis is being performed for nearly every advanced cancer. NGS is at an inflection point, where it no longer serves as a last resort** when all standard therapies have failed but is required before initiating the first systemic therapy for a metastatic cancer…"*

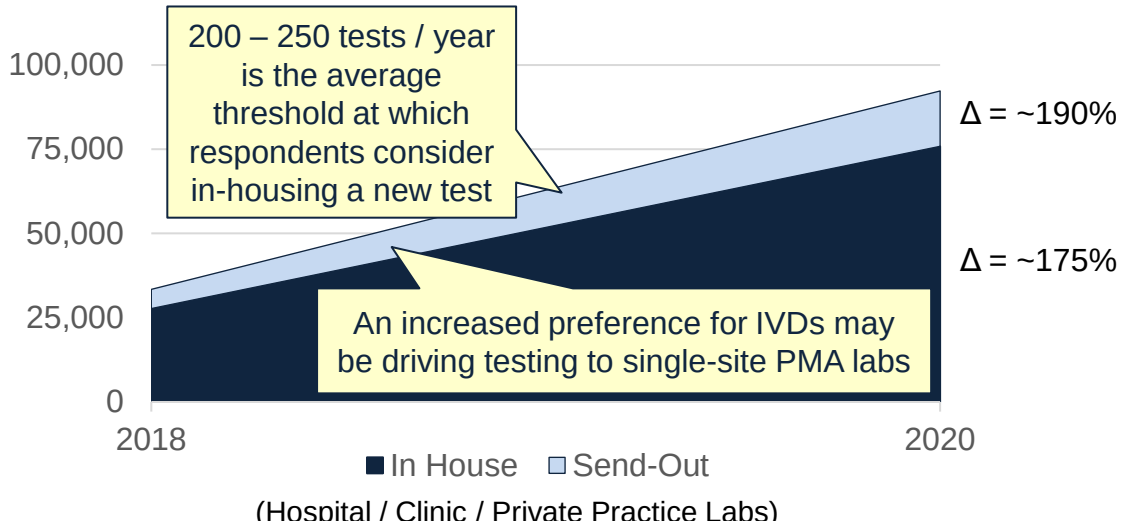
- Oncologist, Private Community Practice

Contrary to prior expectations, outsourcing of testing slightly outpaced insourcing over the past two years; the expectation to adopt emerging biomarker technologies in-house remains limited

For current / established biomarker assays, labs retained a largely stable in-house vs. send-out ratio since 2018, though send-out testing grew slightly faster…

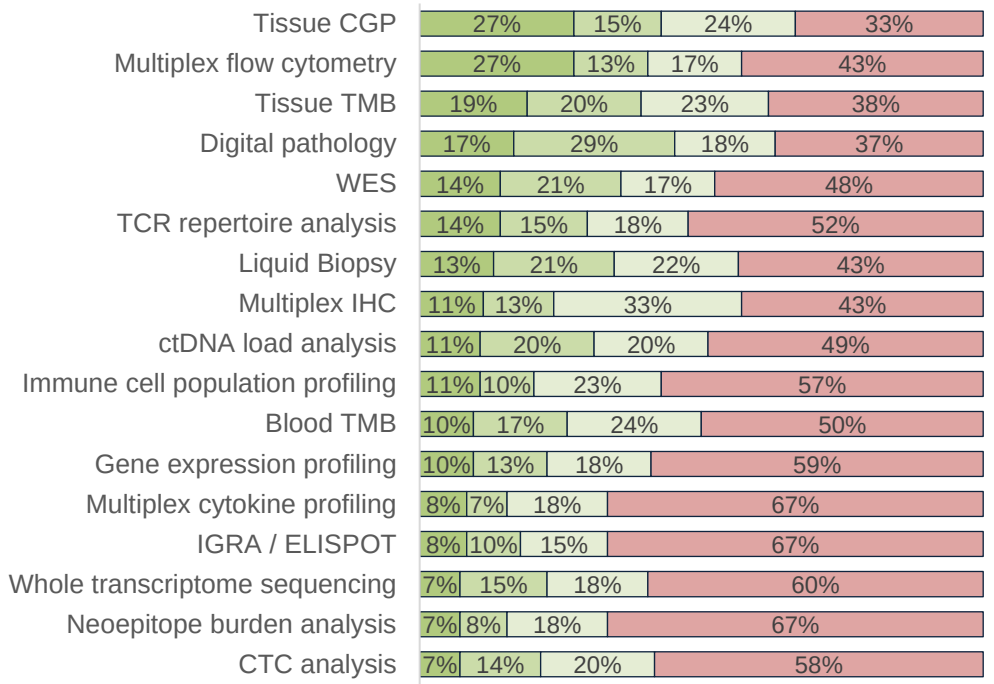
Over the next 2 years, I plan to decrease the amount of testing I send out to reference labs (due to bringing tests in-house)

Assay Volumes, In-House vs. Send-Out 2018-2020



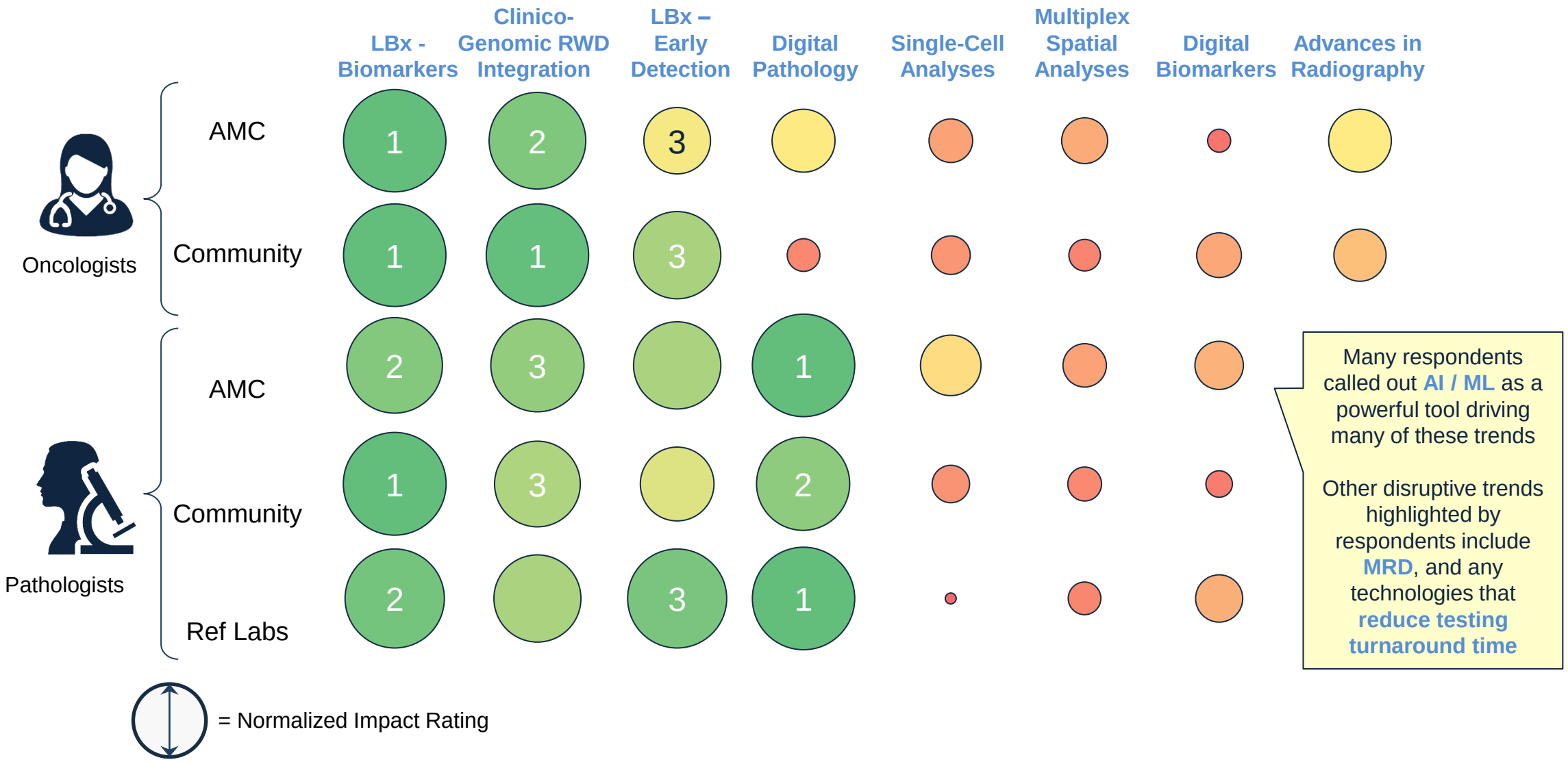
…Outsourcing for emerging / new markers, however, may be high, as many labs do not expect to bring emerging modalities in-house due to equipment capital costs, and validation and requirements

Expected Adoption of a Hypothetical CDx on Emerging Platforms



Respondents cited liquid biopsy as the overall most impactful trend in precision medicine, while pathologists cite digital path as especially impactful; perspectives vary by clinical care setting

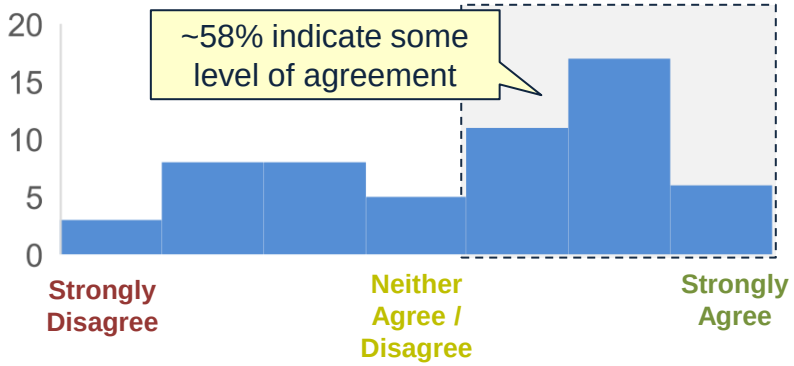
Stakeholder Rankings of Most Impactful Precision Oncology Trends



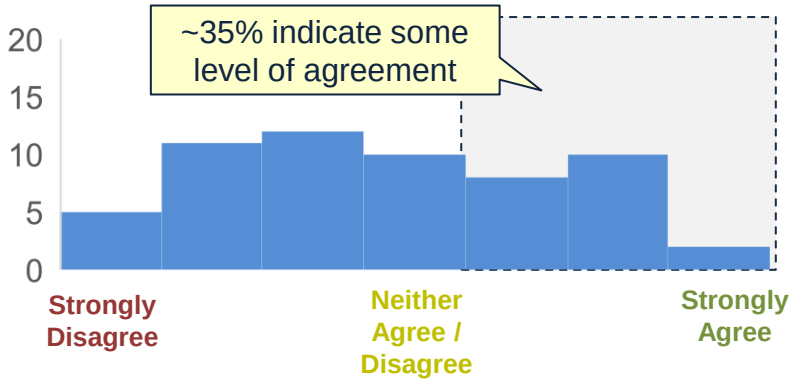
The impact of liquid biopsy in precision oncology is already being felt in routine clinical care today driven by the reduced sampling burden on patients and simpler workflow for clinicians

Confidence in LBx for biomarker testing / CDx is relatively high, while the use of LBx for monitoring is not yet considered as actionable as imaging

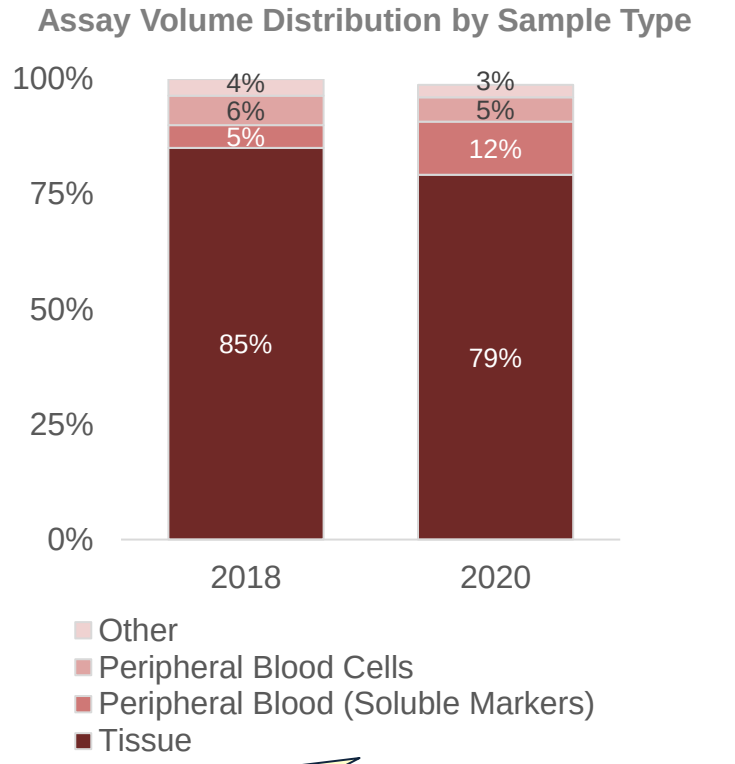
I consider the results of liquid-biopsy testing to be as clinically actionable as those of tissue-based tests



I consider liquid-biopsy based monitoring (e.g., ctDNA loads) to be as clinically actionable as imaging methods



Overall, the share of blood-based testing has increased by nearly ~140% since 2018, but remains <15% of volumes across all markers



Among solid tumor markers / assays, **CGP, MSI, MET, NTRK, PIK3CA** and **TMB** all showed moderate increases in blood-based testing

Interest in LBx remains high, however, due primarily to reduced invasiveness and ease of sampling

"…Less invasive and more precise testing is needed to limit the burden on patients, so liquid biopsies, followed by single cell analyses, will most likely have the edge…"

"…Liquid biopsy, if sensitive and specific enough, should provide non-invasive and maybe more accurate results of mutations due to e.g., tumor heterogeneity…"

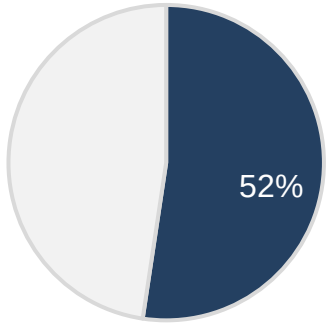
"…Less invasive procedures such as liquid biopsy will become the norm for testing. Easy collection and testing process…"

"…I hope that liquid biopsies are ultimately proven to be as actionable as they are so much more convenient…"

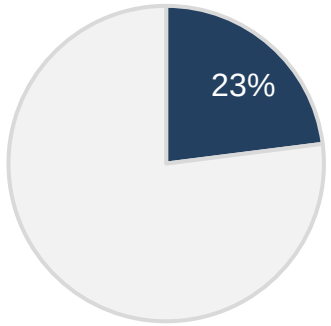
Digital pathology is recognized as a transformative technology with significant clinical potential, though its clinical, financial, and workflow value propositions are still being determined

Approximately half of all labs have digital slide scanners; adoption of computational image analysis solutions is limited (<25% of labs)

Adoption of Digital Slide Scanners (% of labs)

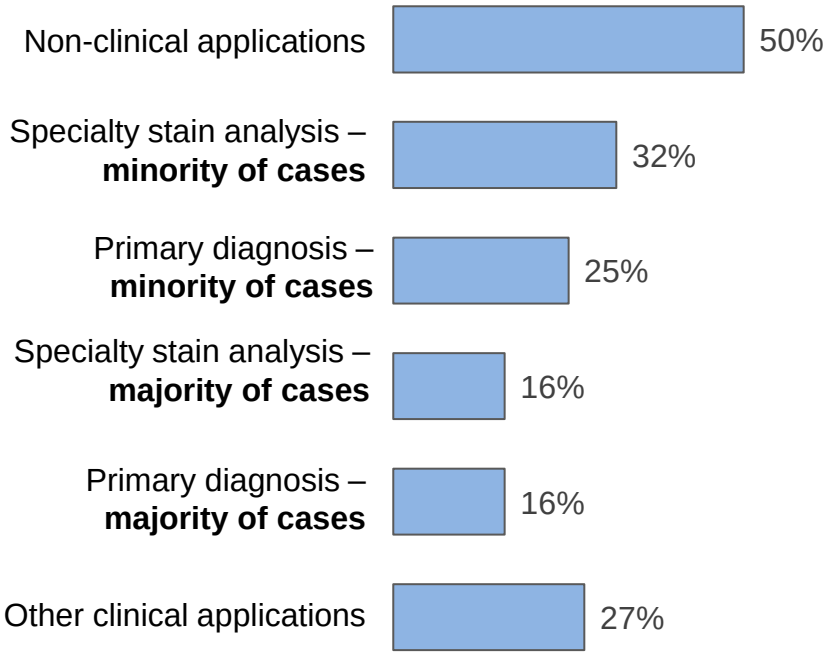


Adoption of Computational Image Analysis Solutions (% of labs)



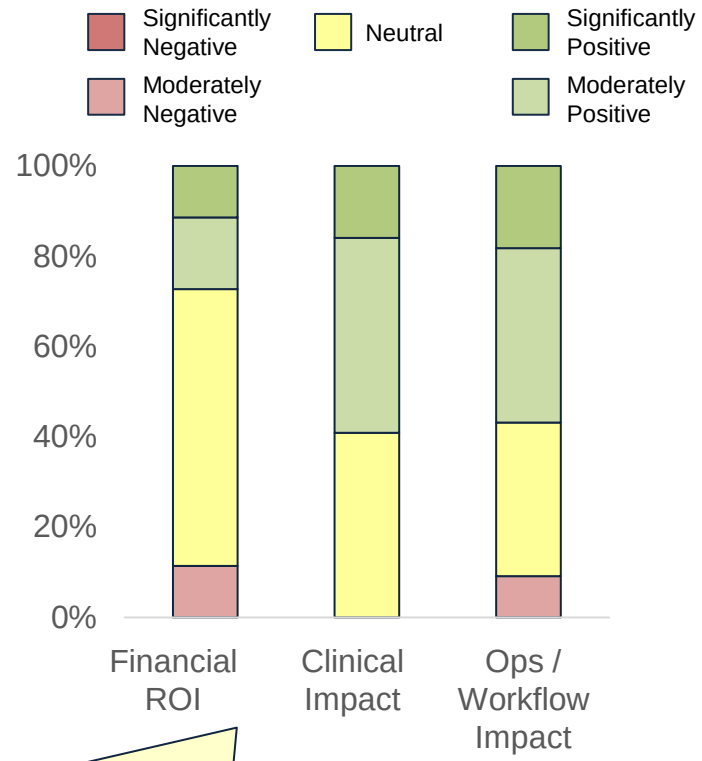
While most lab stakeholders use digital pathology for clinical applications, it is generally used in a minority of cases; non-clinical uses are also common

Digital Pathology Use Cases



Remote consultations / second opinions and use in **tumor boards** were commonly cited key use cases for digital pathology; it was also cited as particularly useful for breast-cancer markers and FISH analyses

The financial, clinical, & workflow benefits of dig. path are largely perceived to be neutral to mod. positive



Many respondents have relatively recently implemented dig. path. (partly due to COVID) and are still evaluating the full extent of its utility

There is high consensus among pathologists that technology is irreversibly changing the field and their role; most are optimistic and nearly all cite a critical need for new skill development in pathology

Pathologist Perspectives on the Future Role of the Pathologist in Precision Oncology

Pessimistic – Decreased Role in Precision Medicine **(~11% of Respondents)**	**Neutral** – New skills will be required for pathologists to succeed **(~48% of Respondents)**	**Optimistic** – Increased Role in Precision Medicine **(~41% of Respondents)**
"…I think that pathology will become more digital soon and computers will replace the humans…"	*"…Pathologists who know molecular will replace the ones who don't..."*	*"…As technology becomes more complex it is critical to have subject-matter experts who understand both the test and clinical entity provide thoughtful interpretation. This is the key role for molecular pathologists and our job is only becoming more important, not less, no matter how good AI gets! (At least for now)..."*
"...At some point, all surgical pathologists will have left is checking margins, and digital pathology will streamline that process…Pathologists need to evolve our value proposition. We should also probably stop training so many pathologists…"	*"…Pathologists must be on board with the changes in technology, especially with respect to AI applications…"*	*"…Now is the hour of the pathologist, I constantly say. All of the complex testing that lies in the lab drives major clinical decisions..."*
"…I feel that general and surgical pathology will have a decreasing role as time goes by due to molecular testing. I'm glad I'm not starting out in Pathology right now, since morphology is what drew me to pathology.…"	*"…With highly multiplexed analysis of tumor slides, pathologist are adapting to a new multidimensional reality…"*	*"… It [role of pathologist] is rapidly changing - increasing responsibilities with clinical, regulatory, financial, administrative duties…"*
	"…A clear and rational integration of clinical, histopathologic, and molecular data is the key challenge for pathologists in the next few years…"	

Based on the trends identified in these data and analyses, we have identified key takeaways for precision oncology market participants and stakeholders to bear in mind when looking to the future

	Theme / Trend	Implications for Stakeholders
1	Surge in precision medicine adoption	• While stakeholders feel comfortable today, education and familiarity gaps remain, and will only grow (and may accelerate) as new biomarkers and integrated data comes online; continued investment in stakeholder education is essential
2	NGS becoming standard of care; expectation of centralization of emerging Dx modalities	• Clinical stakeholders need to be prepared to handle increasingly more data; simplified data management and analysis will become a point of differentiation among NGS providers • Higher utilization will put cost and TAT pressures on NGS providers • Developers of emerging Dx modalities need to consider a service model strategy to maximize accessibility
3	Increasing confidence and utility of LBx	• Many molecular markers (and any other marker for which spatial context is not essential) may shift to liquid-first testing; the establishment of a robust liquid biopsy testing infrastructure will facilitate the adoption of emerging use cases (e.g., screening, monitoring) • Histology will remain a staple of diagnosis / staging, but tissue-based biomarker analyses may become more focused on spatial context than biomarker quantification
4	Moderate adoption of digital pathology with full potential still to be realized	• Digital pathology likely to remain more of a workflow convenience than an essential tool until clearer clinical or operational utility can be established; AI-based computational image analysis expected to be a catalyst for the broader transition to digital
5	Evolving role of the pathologist	• Pathologist education, both in medical school and ongoing education, needs to feature advanced molecular and digital technologies as a core element of training; currently practicing pathologists need to take the initiative to develop these capabilities • It will be incumbent upon emerging biomarker / Dx technology vendors to target pathologists for training and education to maximize clinical adoption

Thank you for your time and attention!

Special Thanks To:

- The PlanetConnect team
- Colleagues at DeciBio who contributed to this analysis
  - DeciBio Analytics' Dexter Platform
- All those who participated in primary research

DEXTER

For more information about DeciBio, visit us at www.DeciBio.com;
These slides will be made available via PlanetConnect; Please connect directly with us for additional insights

Much of the increase in precision medicine adoption is driven by recent drug / CDx approvals, demonstrating relatively rapid uptake of new markers and the expanding precision medicine arsenal

Changes in Biomarker Adoption Rates (Absolute Difference From 2018 to 2020)