Analysis of Effort in Molecular Test Interpretation

Quantitative Survey Data Readout

March 16th, 2021

An AMP report, created with support from AMGEN Oncology

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The evolving molecular test landscape is driving more demand for not only tests but complex interpretation and reporting services.

Growing Demand for Complex Interpretation and Reporting Services

Greater demand for genetic testing

Testing procedure and analysis are becoming increasingly complex

Individualized clinical interpretation of the results is often needed, especially with whole genome sequencing

Reports also must be clearly written and understandable to non-geneticist professionals

Currently interpretation and reporting is completed by both pathologists and doctoral-level clinical laboratory professionals

There are different fee schedules for lab tests and physician services, respectively, with minimal values assigned to interpretation.

Medicare Payment Pathways Summary

Payment Approaches for Testing

Test is primarily a laboratory service

Clinical Laboratory Fee Schedule (CLFS)

- Payment rate is based on historical laboratory charges with the **national rate serving as the ceiling**, resulting in **state-by-state variability**

Current Payment for Interpretation

- CMS intends that codes on the CLFS are inclusive of both technical and interpretive work

Test is primarily a pathologist service

Medicare Physician Fee Schedule (MPFS)

- Payment rate is based on assessment of **time, materials, and other physician expenses** required to execute the test (RVUs)
- Combined (Global) value split into professional component (PC/-26; pathologists time) and technical component (TC)

Current Payment for Interpretation

- G0452 can be used for molecular interpretation (~$50)
- Pathology procedures have interpretation built into the professional component

- **Currently, a separate reimbursement fee for interpretation is only available to pathologists and not to other professionals who perform this activity because it is only available on the MFPS.**
- **Additionally, services on the CLFS are billed by the laboratory entity, while services on the MPFS are reimbursed by the pathologist individually.**

Source: CMS Documents; AMA Documents; ClearView Analysis. RVUs Rates are reevaluated every 5 years by the RUC

ClearView worked with AMP to examine the burden of molecular test data analysis, interpretation and reporting and its impact on lab services.

Project Context

- Currently, molecular diagnostics tests are interpreted by a mixture of health professionals including MD pathologists and PhD geneticists
- The efforts involved in interpretation/reporting of testing are not currently recognized (PhD) or underrepresented (MD) as additional work by payer/reimbursement systems
- This is a damper on investment in the time and effort required to create clear/actionable reports and may be harming patient access to innovative therapies

Project Objectives

Via qualitative research with laboratorians, ClearView Healthcare Partners (ClearView) identified a number of key factors which drive time and complexity in molecular result interpretation

A web-based survey was fielded to the AMP and American College of Medical Genetics and Genomics (ACMG) membership to test quantitatively how data analysis impacts laboratory dynamics

The quantitative research has been analyzed and compiled to support future data driven AMP efforts to engage payers and seek adequate reimbursement

Qualitative and quantitative assessments were conducted to characterize data interpretation / reporting burdens and associated barriers to testing.

Step 1: Kickoff and Align on Objectives

- ClearView engaged in an opening discussion with the AMP Professional Reimbursement Taskforce
- The group aligned on key components related to the project such as tests to include in research

Research Plan for Qualitative Interviews

Step 2: Qualitative Interviews

- ClearView conducted 8 interviews with 4 MD and 4 PhD laboratorians
- ClearView examined the burden of data analysis on the labs and tested hypotheses for how unreimbursed effort impacts the lab

Report of the Qualitative Research

Step 3: Quantitative Online Survey

- ClearView generated an online survey tool that was fielded to the AMP and ACMG lists
- This survey tested impacts of data analysis and hypotheses established in the second step of the project

An Excel File Readout of the Survey Data

Step 4: Synthesis of Findings and Recommendations

- ClearView has analyzed results of quantitative survey to examine trends in how data analysis burdens impact labs
- ClearView has synthesized findings with qualitative interviews to develop strategic recommendations

A Final Report Summarizing Key Findings and Recommendations

Current Step

Source: ClearView Analysis.

AMP is now sharing the results of the quantitative survey.

Qualitative Interviews

- **Qualitative interviews were conducted with laboratorians recruited without regard to AMP membership**

	Planned	Completed
MD	4	4
PhD	4	4
Total	**8**	**8**

- **Interviews with external MD and PhD laboratorians combined with interviews conducted with AMP team members were used to develop the quantitative survey**

Quantitative Survey

- **A quantitative online survey was fielded to AMP and ACMG members with a minimum of 60 respondents targeted for analysis**

	Planned	Completed
MD[1]	30+	35
PhD	30+	61
Other[2]	**NA**	**7**
Total	**60+**	**103**

- **The online survey was distributed through multiple AMP and ACMG listservs from Jul – Sept 2020**

Source: ClearView Analysis. [1] Combines MD/PhD and MD. [2] 5 individuals with master's degrees and 2 with Bachelor's degrees.

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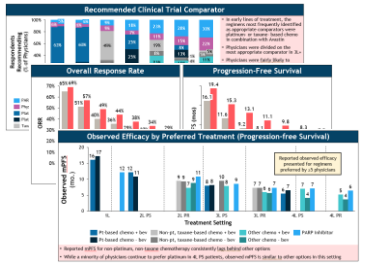
A quantitative survey was fielded after a rigorous process of survey design and refinement.

Quantitative Survey Process

Survey Design	Refine Survey	Conduct Survey	Analysis
			
Aligned on Survey Design with AMP Team	*Soft Launch and Revision Process with AMP team*	*Fielded Online Survey to AMP & ACMG Listserv*	*Compiled Raw Survey Data and Conducted Analysis*

Survey Strategy

- A total of 103 survey results were completed (35 MD, 61 PhD, 7 Other)
- Respondents were asked to answer questions about at least one of the selected tests, but with a request that they enter for multiple tests if possible
- ClearView has analyzed the results of the survey and will make the full survey results and a summary of the findings with potential next steps available to the AMP team

Source: ClearView Analysis.

The following list of tests was used to ensure comprehensive information was collected on a range of test types.

Molecular Diagnostics Examples

Test Method	Test Example	Rational for Inclusion	Test Type
NGS Whole-Genome Sequencing	Rare Genetic Disease Testing (e.g., hereditary developmental defects)	Whole-genome NGS testing represents the currently greatest analysis burden for molecular testing	Genetics
NGS Whole-Exome Sequencing	Rare Genetic Disease Testing (e.g., hereditary developmental defects)	Analysis of mutations and variants from whole-exome sequencing represents a very high analysis burden (e.g., group review)	Genetic
NGS Tumor Panels (5 – 50 Genes and 50+ Genes)	Targeted NGS Panels (e.g., Oncomine, TruSight 500)	Significant analysis required to put specific variant information in a clinical context (could involve tumor board)	Oncology
Multiplex PCR panel	EGFR Mutation Panel for NSCLC	Allows for analysis of multiple potential mutations identified in EGFR with a higher analysis burden than from single loci testing	Oncology
Microarrays	Comparative genomic hybridization for diagnosing genetic abnormalities in children with congenital anomalies	Results obtained from large numbers of loci simultaneously, but lower burden than NGS as all included loci are characterized	Genetics
Somatic Single Loci Testing	BRAF v600e Mutation Analysis in Malignant Melanoma	Example of a single gene cancer assay	Oncology
Germline Single Loci Testing	Testing Known Mutations (e.g., CFTR mutations for cystic fibrosis)	Example of a single gene hereditary analysis with variable complexity given the inclusion of dup/dels, etc.	Genetics

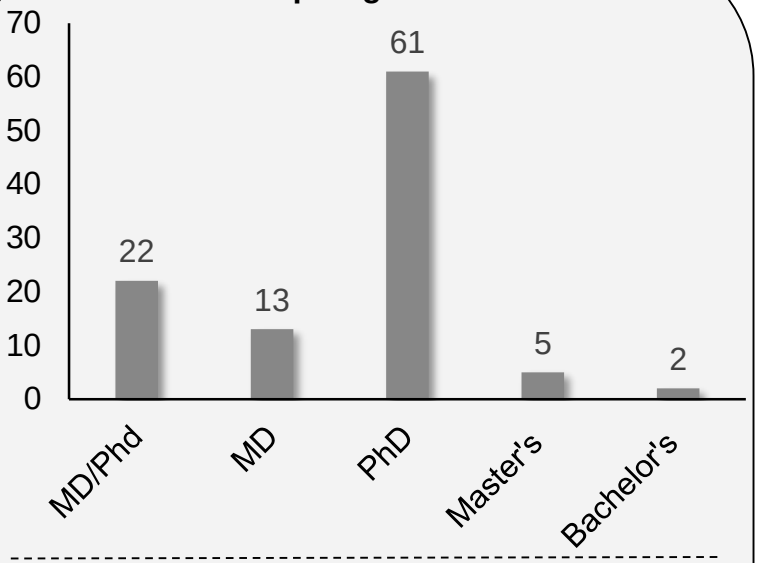
Tests were selected to represent a mix of oncology and human genetics tests that span a wide range of complexities from single gene PCR to whole-genome sequencing

Source: ClearView Analysis. NGS: Next generation sequencing. NSCLC: Non-small cell lung cancer.

The survey was taken by a mixture of laboratorians, with most respondents working at academic centers and holding ABP or ABMGG certifications.

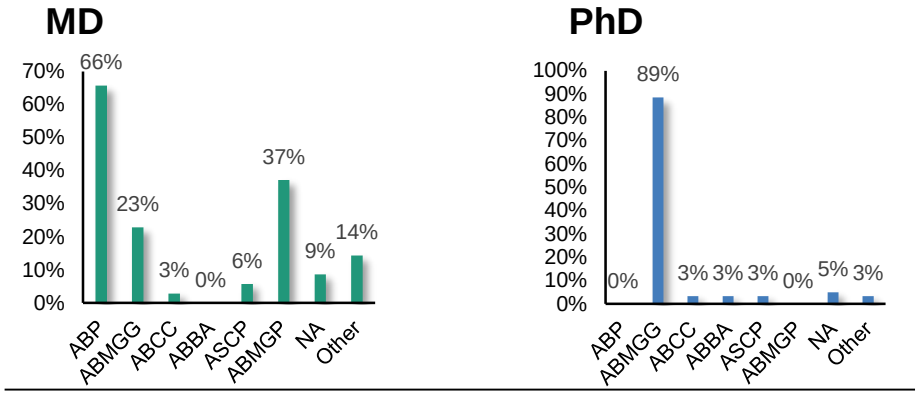
Respondent Information

Top Degree Held

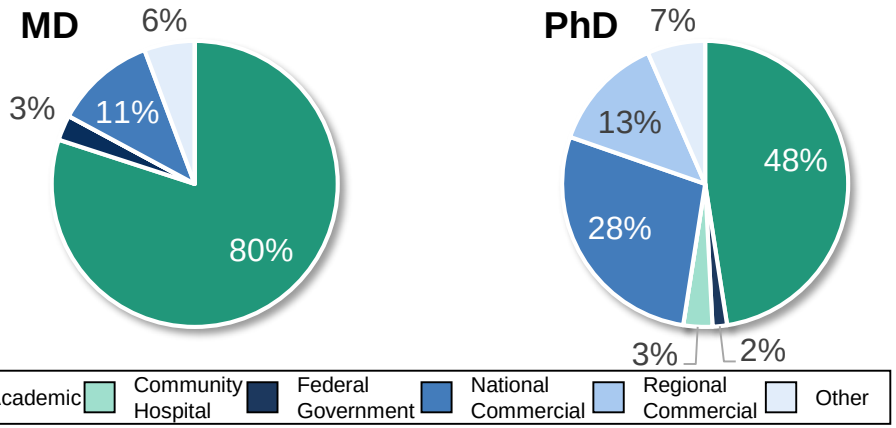


- 35 responses were recorded from **MD/PhDs and MDs** that **were classified as MD unless otherwise noted**
- 61 PhDs responded to the survey
- 7 responses were recorded from **master's and bachelor's degrees** that **will not be counted in MD/PhD breakdowns**

Professional Certifications Held



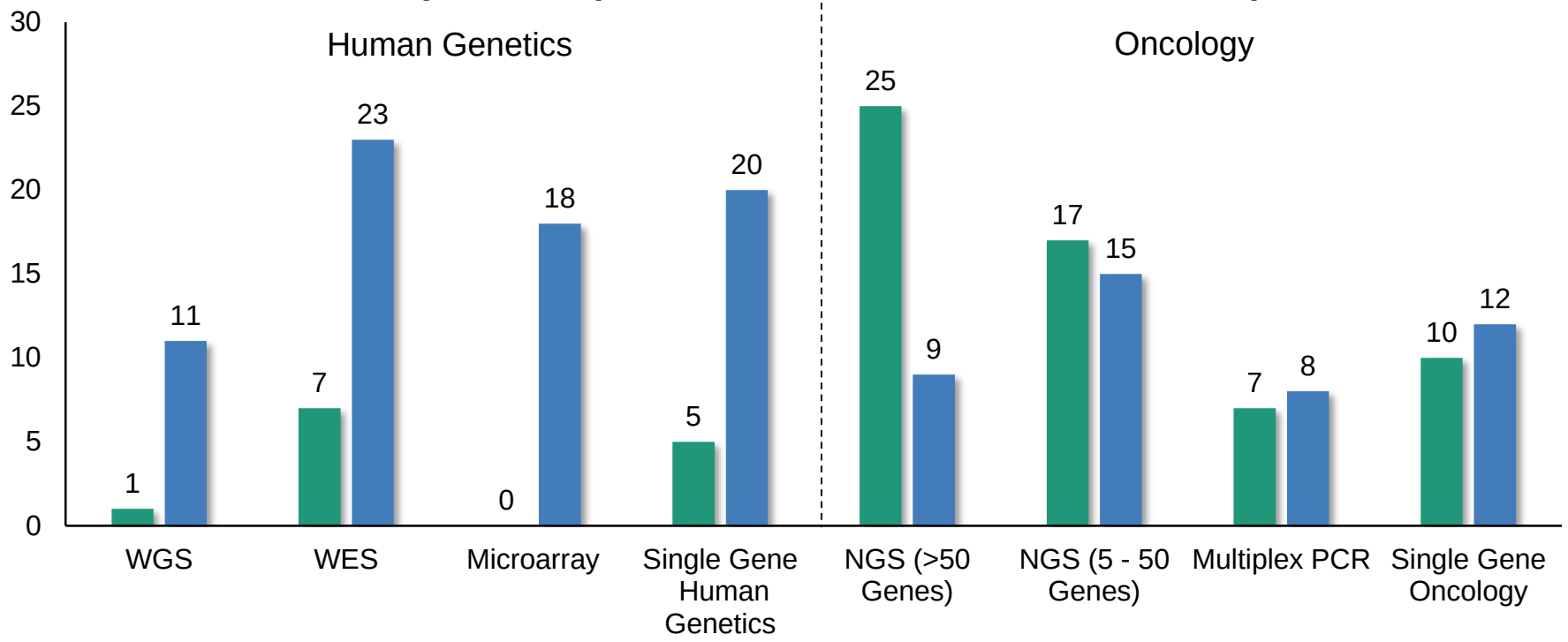
Institution Type



Source: Laboratorian Survey; ClearView Analysis. ABP: American Board of Pathology; ABMGG: American Board of Medical Genetics and Genomics; ABCC: American Board of Clinical Chemistry; ABBA: American Board of Bioanalysis; ASCP American Society for Clinical Pathology; ABMGP: American Board of Molecular Genetic Pathology.

While PhDs are more involved with human genetics tests, both MDs and PhDs are similarly involved with oncology tests.

Respondents selected tests that they perform and for which they are comfortable answering questions about the interpretation process and reimbursement landscape.



	WGS	WES	Microarray	Single Gene Human Genetics	NGS (>50 Genes)	NGS (5 - 50 Genes)	Multiplex PCR	Single Gene Oncology
Total	*12*	*30*	*18*	*25*	*34*	*32*	*15*	*22*

WES, WGS, and microarray showed more PhD involvement while MDs indicated more involvement in oncology testing, especially NGS testing

N=72 MD responses and 116 PhD responses, for an average of ~2 responses per individual

Source: Laboratorian Survey; ClearView Analysis.

Key: MD PhD

In our sample, national commercial laboratories had higher volumes for nearly all assays and especially NGS 5 – 50 gene panels.

Average Testing Volume per Month

	WGS	WES	Microarray	Single Gene Hum Gen	NGS 5 – 50 Genes Oncology	NGS >50 Genes Oncology	Multiplex PCR Oncology	Single Gene Oncology
Academic	29 *(12%)*	84 *(11%)*	95 *(9%)*	466 *(8%)*	65 *(>1%)*	141 *(10%)*	26 *(56%)*	34 *(15%)*
National Commercial	145 *(65%)*	515 *(68%)*	719 *(68%)*	4,354 *(74%)*	8,249 *(99%)*	951 *(68%)*	11 *(24%)*	140 *(63%)*
Regional Commercial	0	106 *(14%)*	45 *(4%)*	1026 *(18%)*	41 *(>1%)*	293 *(21%)*	9 *(20%)*	50 *(22%)*
Other	51 *(23%)*	50 *(7%)*	200 *(19%)*	0	0	0	0	0
Total	225	755	1,059	5,846	8,355	1,385	46	224

Source: Laboratorian Survey; ClearView Analysis.

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The analysis, reporting, and interpretation process was explored in detail in the survey.

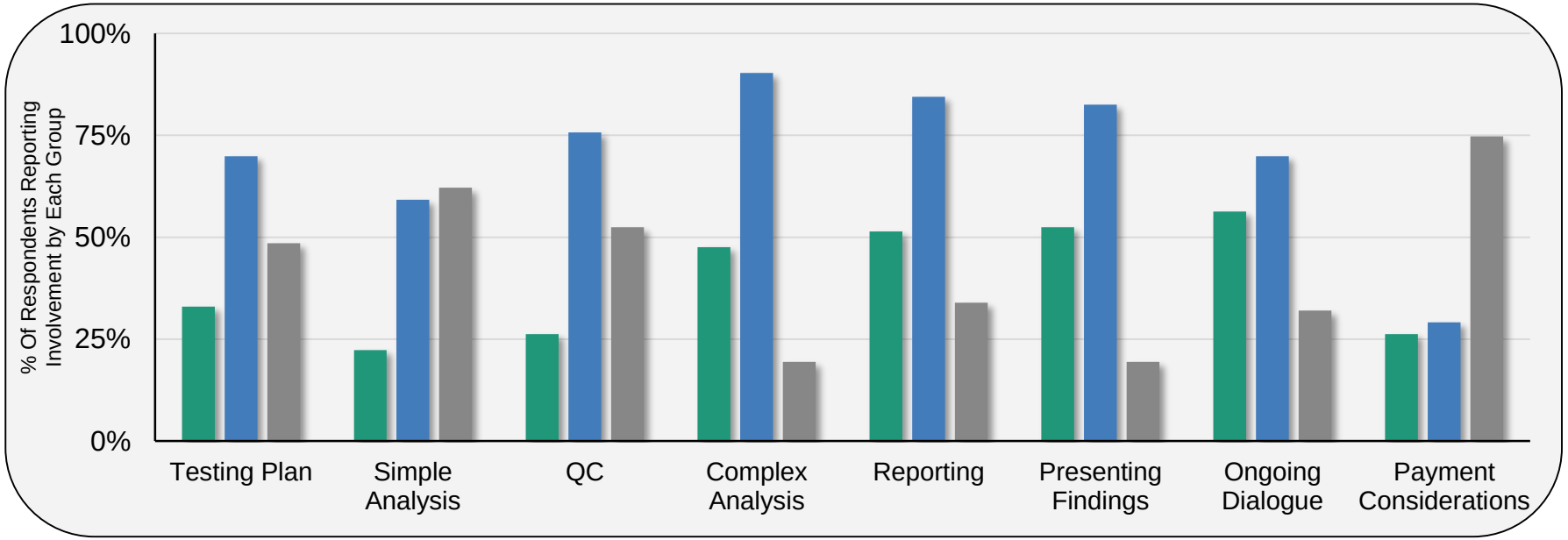
Steps in Analysis, Reporting, and Interpretation Process Included

Testing Plan and Pre-Analytics	Confirming appropriate test order, evaluating sample collection methods, consulting with ordering physicians on alternative tests
Payment Considerations	Confirming prior authorization with insurance companies, determining if reimbursement is sufficient, negotiating reimbursement, etc.
Simple Analysis	Reading gels, slides, plots, etc., aligning sequences
Quality Control	Confirming that test is within parameters, appropriate control results, and any other steps needed to QC initial test data
Complex Analysis	Researching genetic variants, identifying relevant clinical literature, researching potential treatment options, etc
Reporting	Combining multiple test results, considering clinical history with testing results, writing/reviewing the final testing report
Presenting Findings	Presenting findings at molecular tumor boards or similar physician conferences
Ongoing Dialogue	Explaining test results to ordering physicians, discussing potential follow-on tests, discussing clinical literature, etc.

Source: ClearView Analysis.

Both MDs and PhDs are heavily involved in each step of molecular testing analysis, interpretation, and reporting.

In your laboratory, who is usually involved in each step in this process (MD, PhD, or Other?) *Please select all that apply*



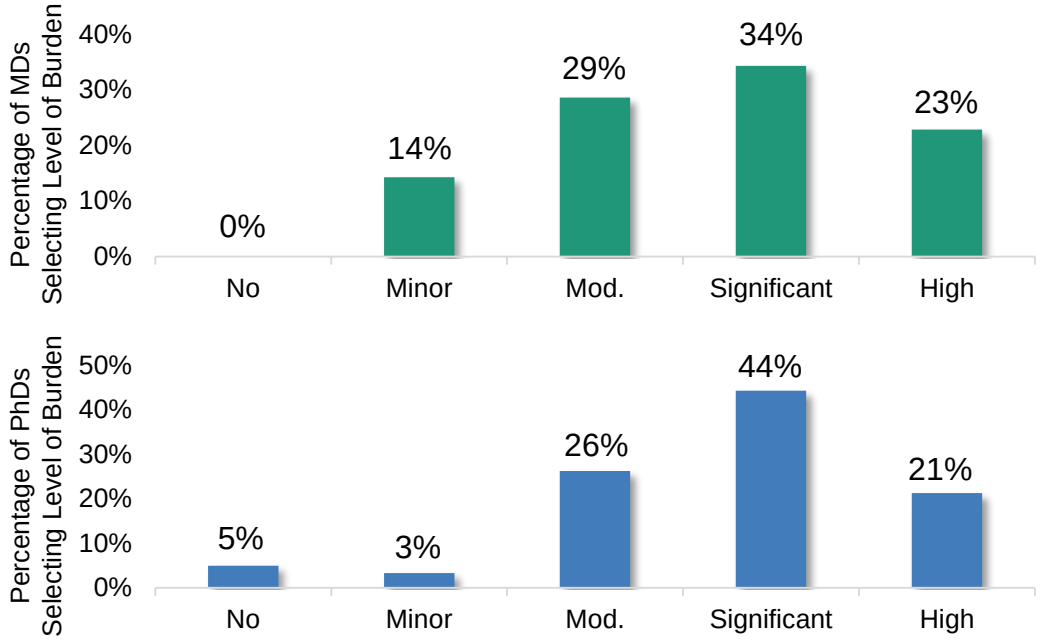
- Respondents report **reasonably even engagement from MDs** with a low of ~20% in simple analysis and a high of ~55% in ongoing dialogue
- While PhD involvement was high in all areas, it was more focused in later steps, with 75%+ of respondents reporting **PhD involvement in complex analysis, report generation, and presentation**
- **Other personnel** are commonly used for **early QC and simple analysis** or **reimbursement process**

Source: Laboratorian Survey; ClearView Analysis.

Key: MD PhD Other

Respondents classified the burden of analysis, reporting and interpretation relative to other lab tasks and ranked the steps by time commitment.

Relative to other laboratory functions, how would you rate the time burden due to molecular diagnostics data analysis/reporting?
Please select one



Please rank order the steps below in terms of time commitment for your laboratory (*1 representing the highest burden and 8 the lowest*)

Analysis Step	MD	PhD
Complex Analysis	1.7	1.7
Generating Reports	3.0	3.1
Initial Analysis	4.2	3.7
Data QC	4.9	4.9
Presenting Results	5.0	5.3
Testing Plan	5.5	5.3
Ongoing Comm.	5.5	5.6
Payment Issues	6.1	6.2

- **Analysis and reporting was considered a significant burden** for labs relative to other functions, with ~65% selecting significant or high burden
- The **primary driver of effort is the complex analysis step** for molecular testing
- MDs and PhDs had **similar perceptions of the burden and effort** involved in analyzing molecular tests

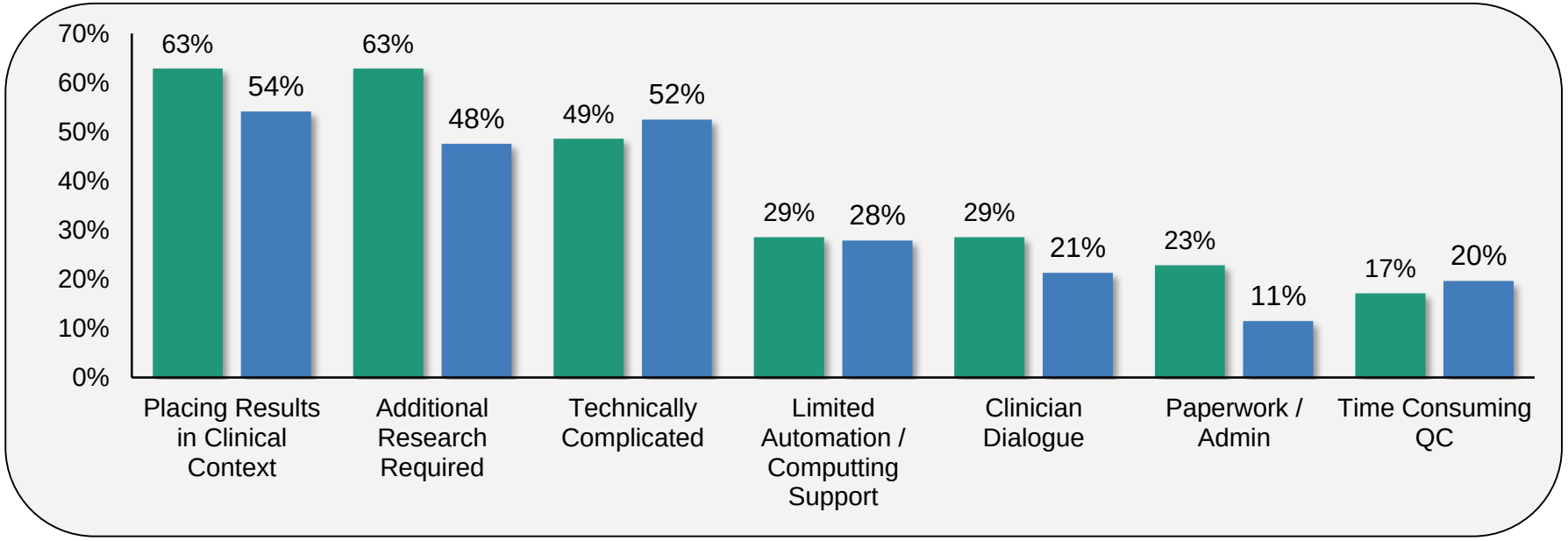
Source: ClearView Analysis.

Key: MD PhD

Clinical interpretation, additional research requirements, and technical complexity were the major drivers of effort for MDs and PhDs.

For the step listed as most effort, please select why it is the most effort.

Please select all answers from the below list that you consider a major contributor to the effort required.



- **Technical complexity, additional research requirements, and placing test results in context** were the **most commonly noted reasons** for extra effort being required in analysis and interpretation
- MDs and PhDs selected the same 3 factors as the main focuses of their effort

Source: Laboratorian Survey; ClearView Analysis.

Key: MD PhD

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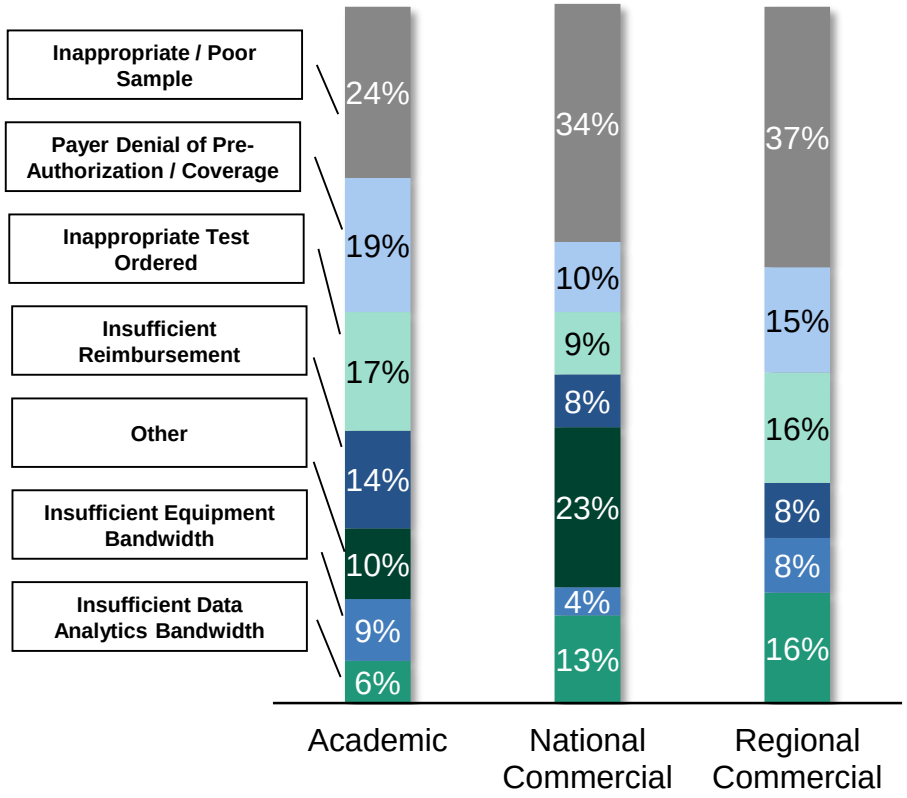
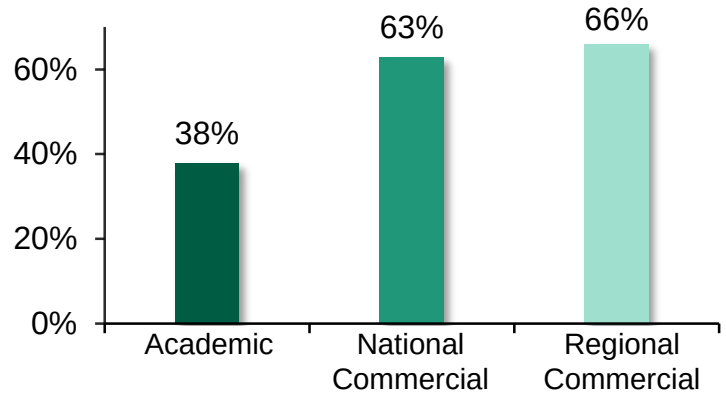
Issues related to sample quality / test selection drive most uncompleted tests and may increase communication burdens on labs related to samples.

Of tests that are ordered from your laboratory but not run in-house, what percentage of the time are they not done for the following reasons?
Please enter an integer number between 0 - 100

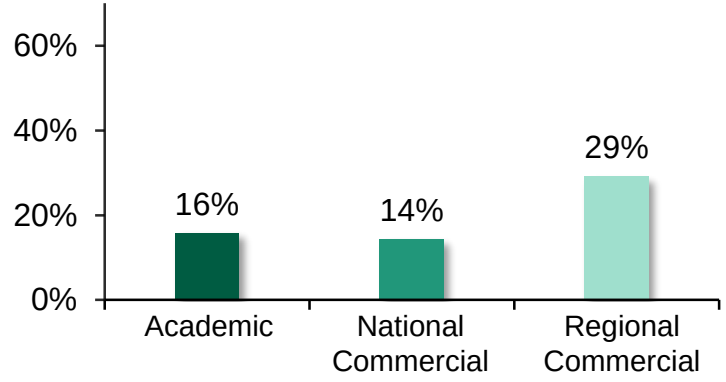


Source: Laboratorian Survey; ClearView Analysis.

What percentage of communication with ordering physicians is handled by non-doctorate level staff?
(*e.g., caseworkers, clinical sciences liaisons, genetic counselors*)?

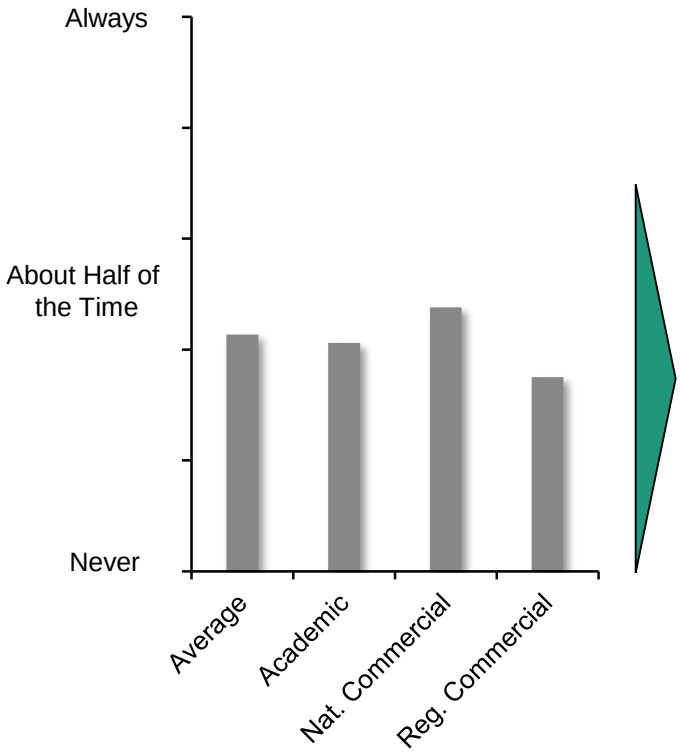


For what percentage of tests do you or someone in your lab decide to replace a test with a significant data analysis component with a less intensive one that may provide similar data?

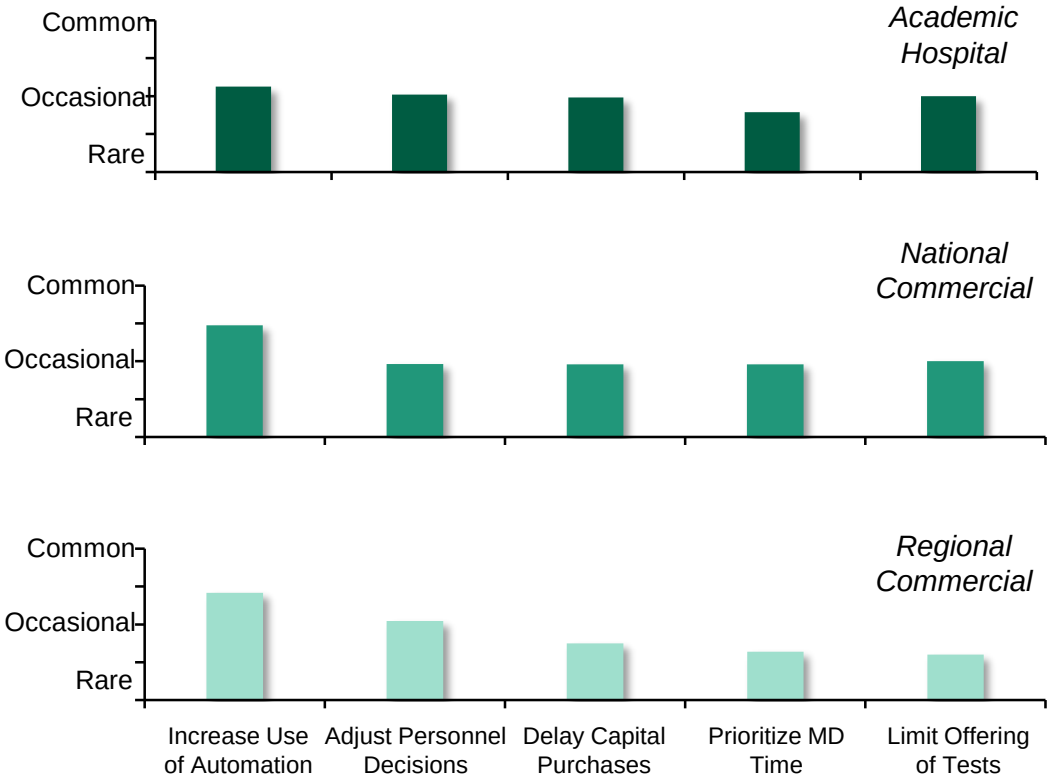


Survey responses suggest similar frequencies of analysis burden impacting testing decisions and similar strategies for managing the burden.

How frequently, if ever, does the time burden related to analysis of molecular diagnostics data influence testing decisions (e.g., when to run a test, which test to run, to run in house or send out to another laboratory) in your laboratory? *Please select one choice*



Has your lab undertaken any of the below steps to manage the impact of data analysis and reporting requirements?
Please select one choice

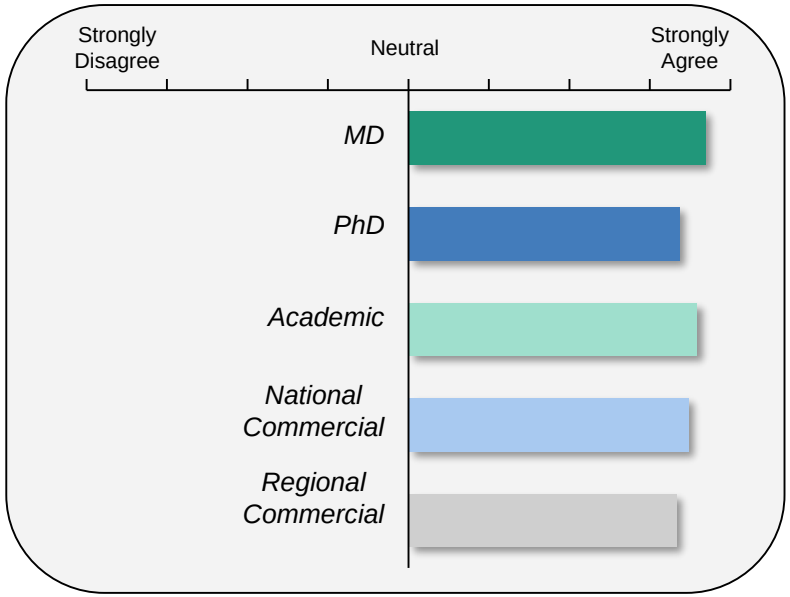


Source: Laboratorian Survey; ClearView Analysis.

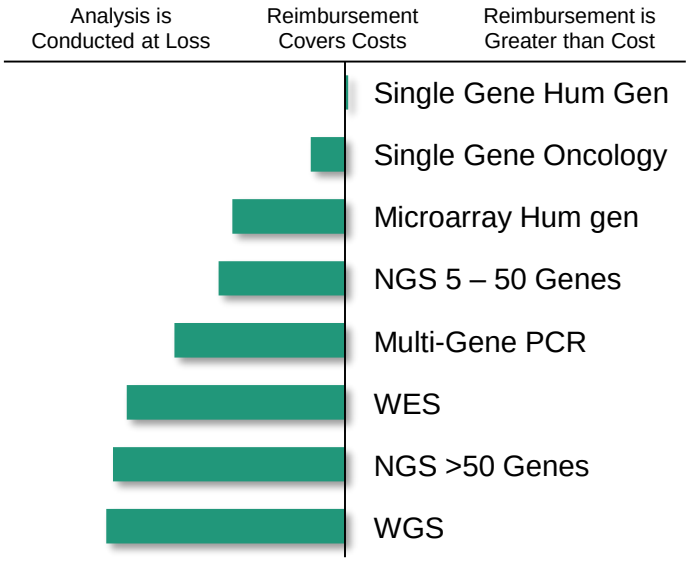
Respondents were asked to rate their personal agreement with the view that reimbursement for analysis, reporting, and interpretation is insufficient for the time they spent performing these activities.

Responses to "Effort spent on data analysis/reporting is NOT sufficiently reimbursed relative to the effort and time commitment required. "

Agreement with Statement



Reimbursement of Analysis for Individual Tests

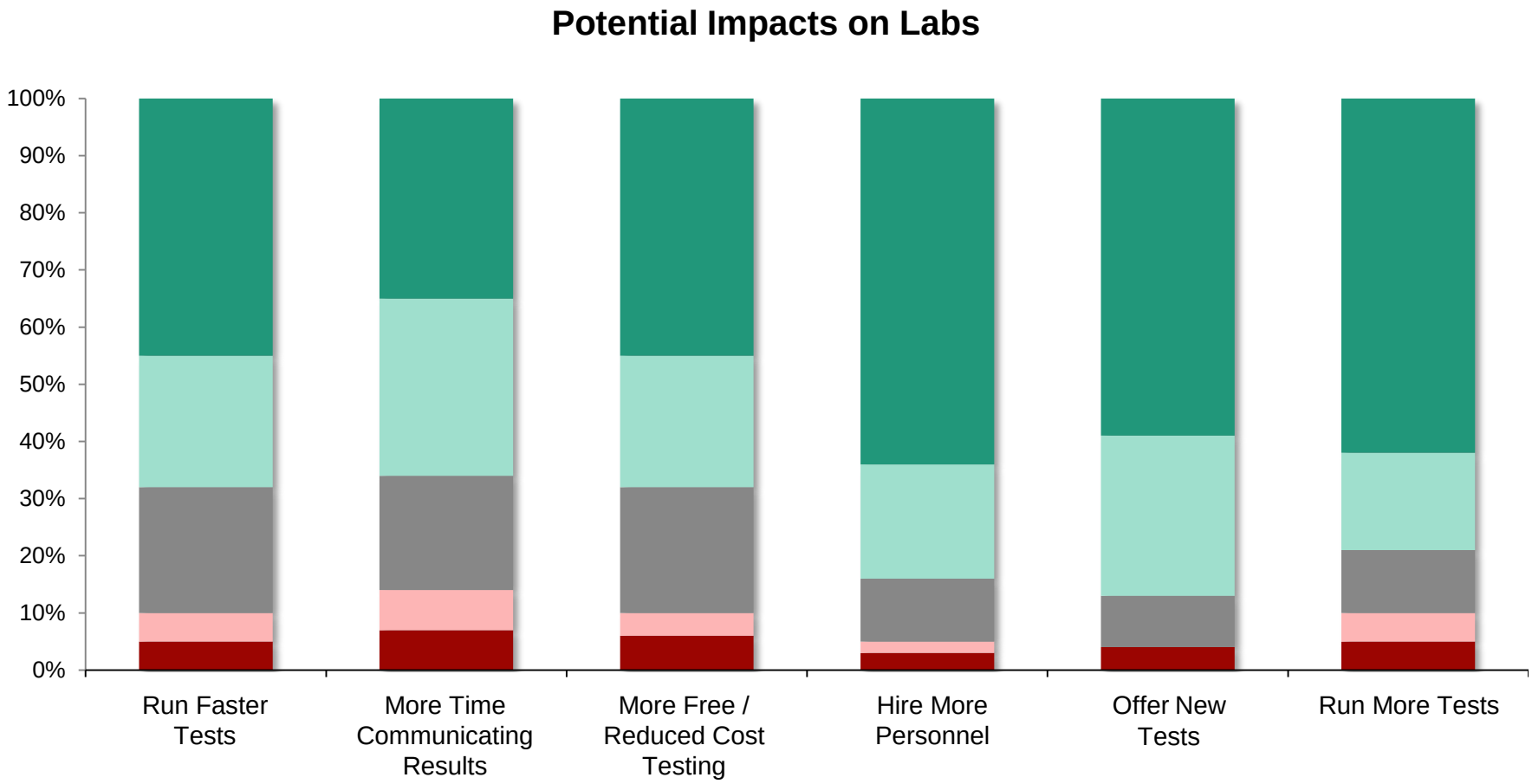


Data analysis and reporting was viewed as insufficiently reimbursed by MDs and PhDs in academic and commercial settings

Only single gene tests for human genetics were considered to not result in a loss based on analysis, interpretation, and reporting

Source: Laboratorian Survey; ClearView Analysis.

If reimbursement was sufficient for the time spent, laboratory professionals indicated that they would offer new tests, hire more personnel and run more tests.

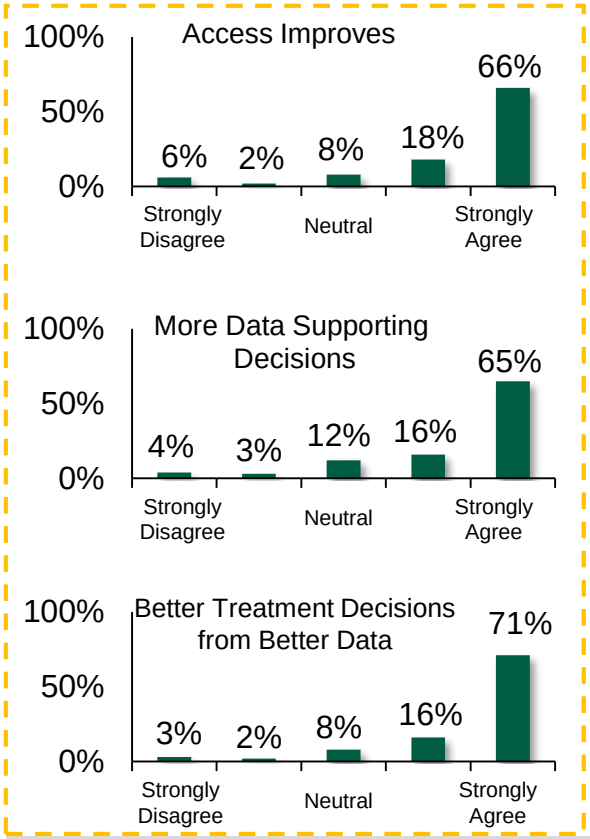


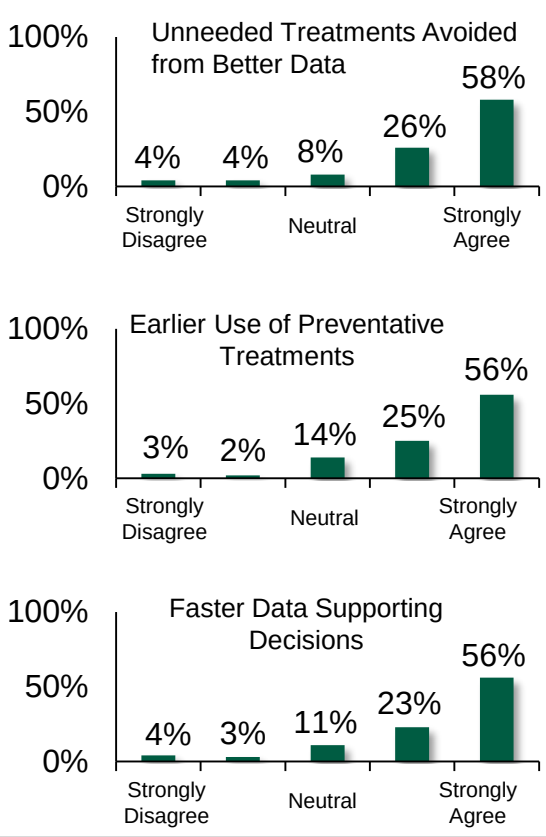
Improvements in function were anticipated by a majority of respondents who are expecting gains in all areas and additional confidence in new testing, more testing, and more personnel

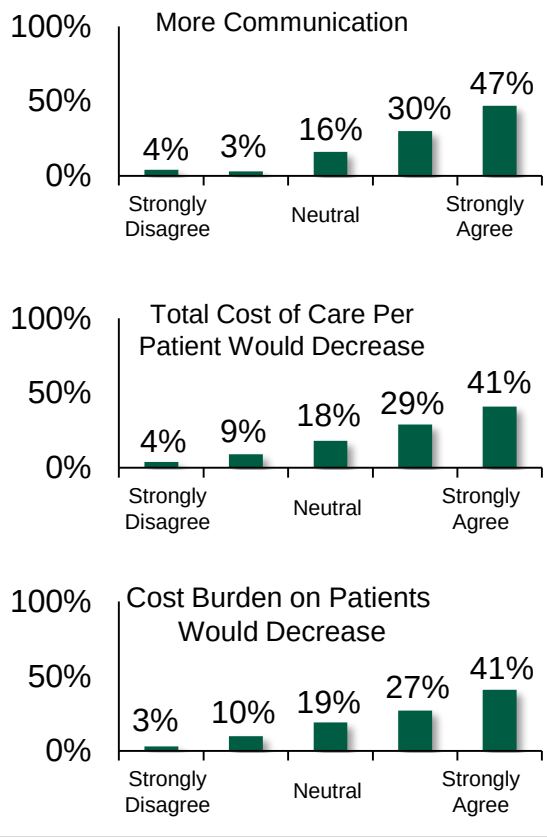
Source: Laboratorian Survey; ClearView Analysis.

Questions were asked of respondents to assess the likelihood of improvements in the patient-related factors from adequate reimbursement.

Potential Impacts on Patients







Respondents strongly agreed that access, data, and decision making would improve from better reimbursement for analysis and reporting while there was less confidence in cost reductions

Source: ClearView Analysis.

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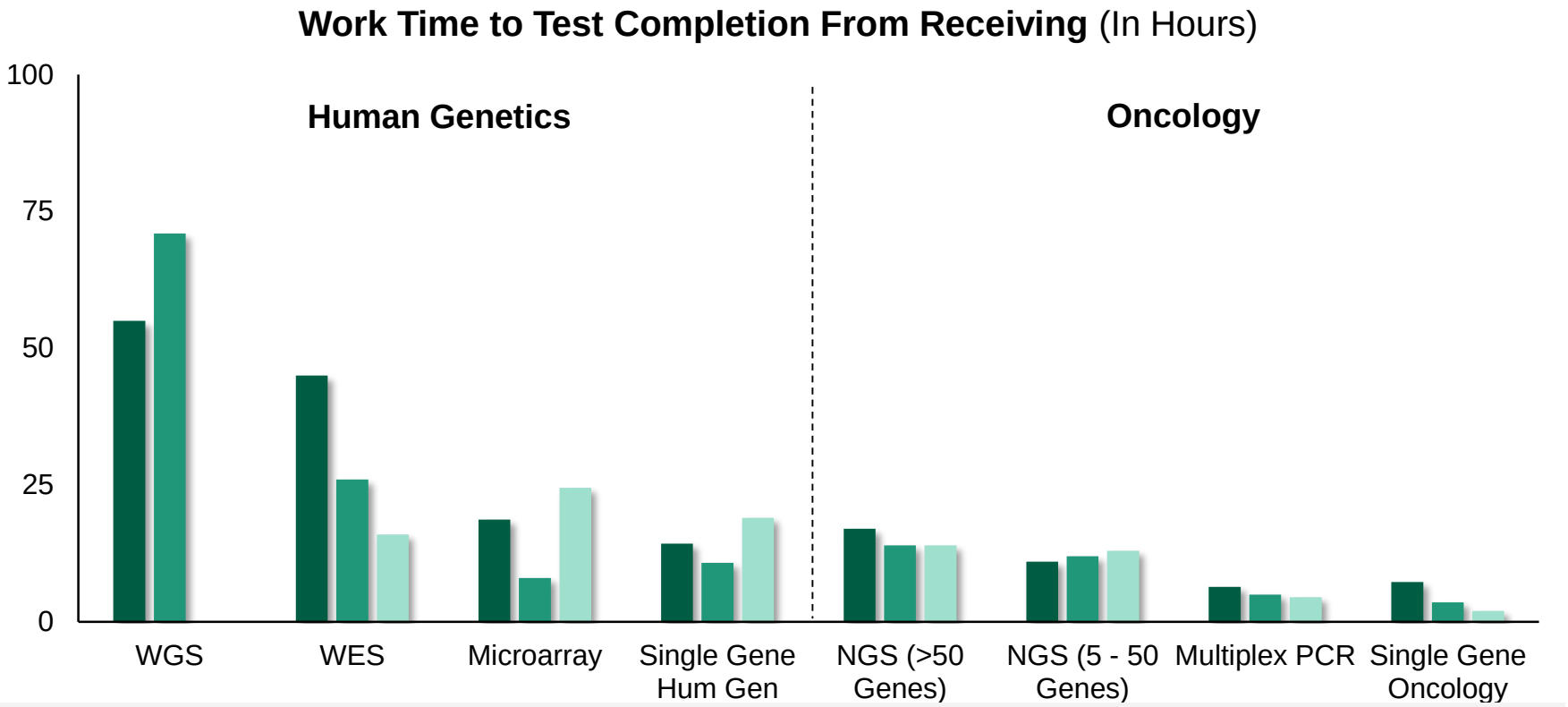
Laboratorians were asked to estimate the time to test completion from receiving the samples for the selected assays.



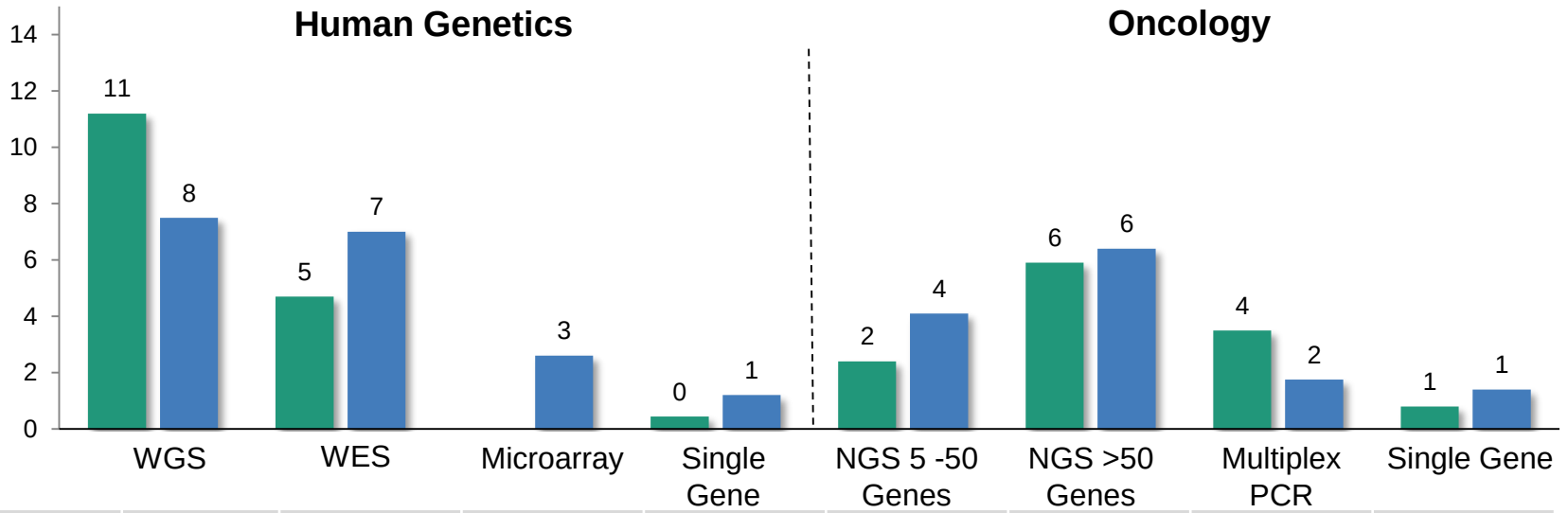
- **Little difference was seen across different institution types** though academic labs were generally slightly slower and national commercial labs slightly faster, with WGS as an exception
- **Time to complete tests** showed **analysis heavy tests WGS and WES standing out** significantly from other assays considered and **oncology generally being delivered faster than human genetics**

Source: ClearView Analysis.

Key: Academic | Nat. Commercial | Reg. Commercial

PhDs and MDs reported the time that they spend for each test type selected with more PhD time on genetics and more MD time on oncology noted.

Average Time Per Test by Laboratorian Type (Hours Adjusted for Batch Size)



	WGS	WES	Microarray	Single Gene	NGS 5 -50 Genes	NGS >50 Genes	Multiplex PCR	Single Gene
# of MDs (%)	1 (10%)	7 (25%)	0 (0%)	9 (45%)	17 (57%)	18 (78%)	4 (33%)	5 (21%)
# of PhDs (%)	9 (90%)	21 (75%)	17 (100%)	11 (55%)	13 (43%)	5 (22%)	8 (67%)	19 (79%)

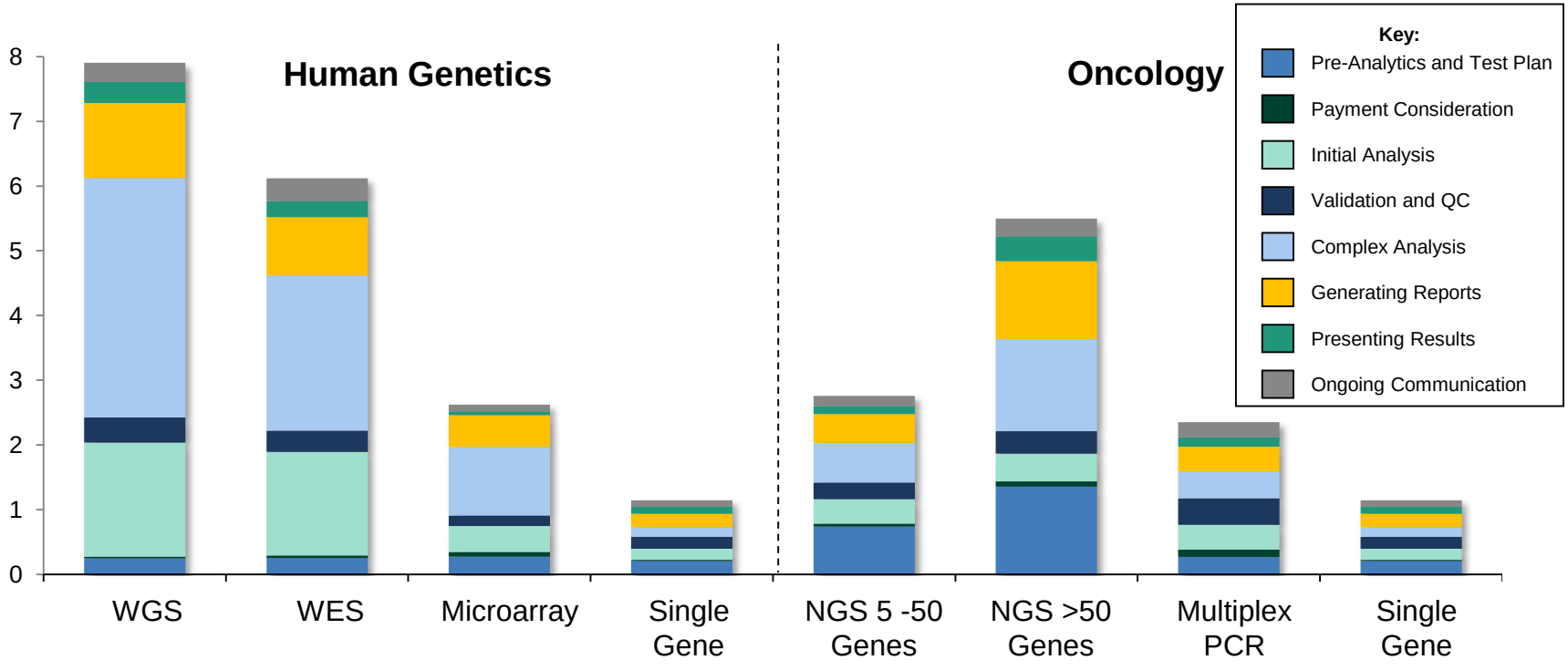
- **WGS and WES techniques were noted as the most time-consuming, along with NGS >50 Genes,** averaging **7 – 9 or 6 hours of effort, respectively,** related to data analysis, interpretation, and reporting
- **PhD time** spent was noted as significantly **greater than physician** time for **WES and, of respondents, only PhDs conducted microarray analysis**

Source: Laboratorian Survey; ClearView Analysis. 1 Responses were adjusted for tests performed in batches

Key: MD PhD

Respondents were asked to estimate the average time commitment per step of the analysis and reporting process for each selected molecular test.

Average Time Per Step by Test Type (Hours Adjusted for Batch Size)



- **Significant variability** exists in **time commitment per step** of analyzing and reporting molecular tests
- **Initial and complex analysis** require the greatest time **commitment for human genetics tests** (e.g., WGS, WES), while **complex analysis and pre-analytics/test plan** are the greatest commitments **for NGS** panels

Source: Laboratorian Survey; ClearView Analysis. [1] Responses were adjusted for tests performed in batches and averaged across the total sample.

These numbers compare favorably to the finding from the qualitative research.

Qualitative Survey Findings: Stakeholder Reported Time Burden by Analysis Step[1]

	Testing Plan	Initial Analysis	Validation and QC	Complex Analysis	Reporting	Presenting Results	Ongoing Dialog
Whole - Genome	0.5 – 10 Hours	1 – 8 Hours	1 – 4 Hours	4 – 40 Hours	0.5 – 8 Hours	0 – 4 Hours	0 – 4 Hours
Germline Single Loci	0.1 – 10 Hours	~0.5 Hours	<0.5 Hours	0 – 1 Hours	0.5 – 8 Hours	0 – 4 Hours	0 – 4 Hours

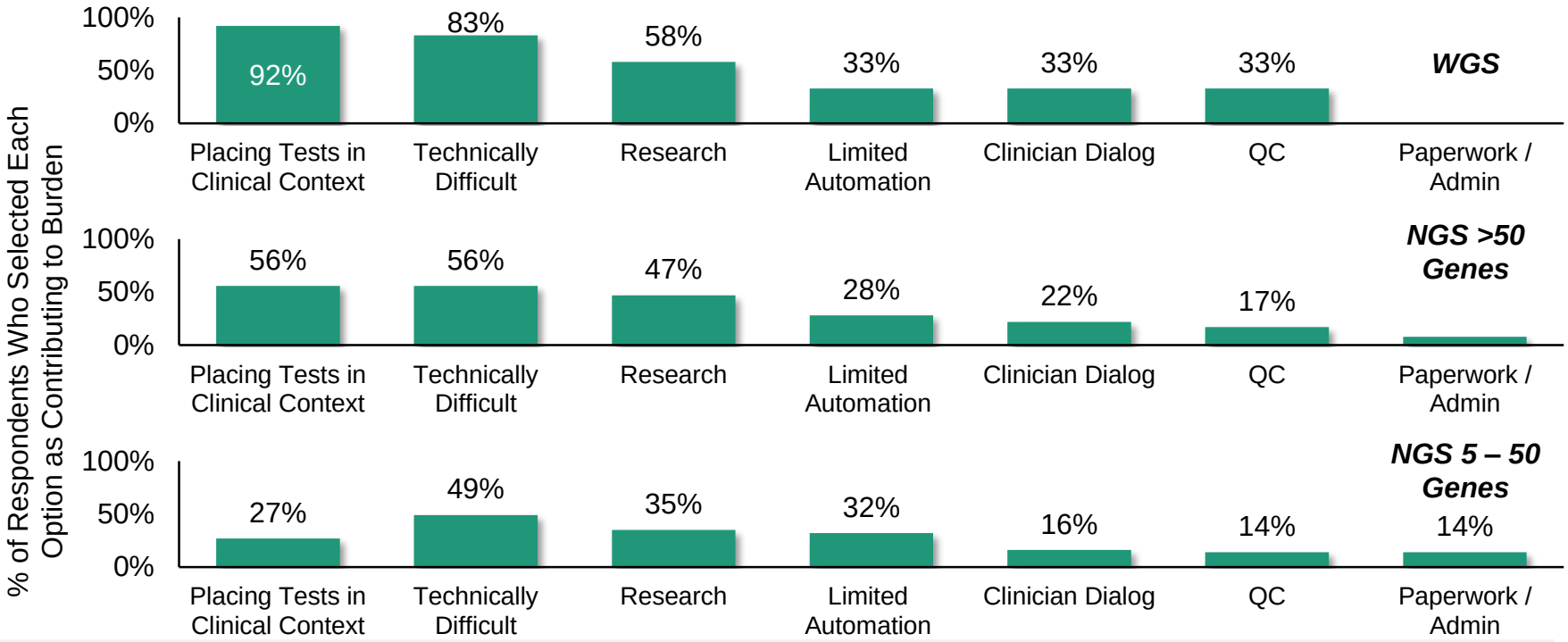
Key Findings

- The amount of time spent on individual steps was similar between practitioners; however, respondents noted that MDs and PhDs may perform different tasks more frequently
- Potential min and max time per tests are similar, though averages for specific use cases will be captured through the quantitative survey

Source: ClearView Analysis. [1] Values represent minimum and maximum values reported in the qualitative interviews.

Laboratorians were asked to identify pain points that contribute to time burdens associated with the analysis and reporting of molecular tests.

Factors Identified as Contributing to Burden for Top Three Time Requiring Tests



- **Technical difficulty, additional research requirements, and placing tests in clinical context** were consistently rated as the **greatest drivers of time burdens** related to analysis and reporting
- More complex genetic tests are notable for their **technical difficulties and integration of results into the clinical context** (potentially requiring greater clinical judgement and experience)

Source: Laboratorian Survey; ClearView Analysis.

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MDs and PhDs conduct similar functions in labs, consider reimbursement low for professional work, and often devote >6 hours to a single test.

Key Findings

Responsibilities of MDs and PhDs within laboratories largely overlap	MDs and PhDs both reported similar levels of participation in laboratory functions related to the analysis, interpretation, and reporting of molecular tests and participation in most tests surveyed
A higher proportion of MD respondents reported involvement in oncology tests	A higher proportion of PhD respondents reported involvement in non-oncology tests
All respondents reported that reimbursement for analysis, interpretation, and reporting is too low compared to effort	All types of respondents rated reimbursement for the analysis, interpretation, and reporting process to be generally insufficient, as well as highlighted that the situation was worst for complex tests such as WGS, large NGS panels, and WES
The amount of time that can be required in the analysis, interpretation, and reporting process is substantial	The average time commitment devoted to analysis, interpretation, and reporting for complex tests such WGS, WES, and large NGS panels was reported to be 6 – 8 hours

Source: ClearView Analysis.

Survey findings further compound current trends in molecular diagnostics with negative impacts on laboratories and downstream patient care.

Key Implications

1 Insufficient Reimbursement Hinders Molecular Testing

- The survey revealed that adequate reimbursement would enable laboratories to improve access to testing, resulting in more ordering physicians being able to make more informed treatment decisions

2 As More Complex Molecular Tests Become Standard of Care, Burdens on Laboratory Professionals Will Be Exacerbated

- Increasing utilization in complex testing paradigms, such as WGS, WES, and NGS will likely result in higher analysis, interpretation, and reporting burdens in the future

3 Laboratories Indicated That They Are Already Taking Steps to Reduce Negative Impacts of Insufficient Reimbursement

- The survey demonstrated that labs are using more non-doctorate case managers for communication, limiting the number of tests offered, and sending out tests to manage costs

4 Limitations in Reimbursement May Lead to Consolidation of Testing to a Smaller Number of Laboratories and Limit Patient Access

- Current trends may push community labs to not perform molecular tests with limited reimbursement which may push this testing to academic and national reference labs
- In this scenario, academic and large labs could be stressed by an influx of poorly reimbursed tests that other labs no longer conduct

Source: ClearView Analysis.

Obtaining additional data to incorporate additional stakeholders' perspectives before approaching payers may bolster AMP's evidence package.

Recommendations and Potential Next Steps

- Develop internal and external informed perspectives on the future testing landscape to leverage with this material to forecast future analysis burdens on labs
- Explore case studies from internal and external laboratories on how existing analysis burdens impact laboratory function and how this will increase with anticipated changes
- Engage with physician and patient groups to better define negative outcomes from slow, expensive or insufficient testing
- Develop and advocate for policy changes that will positively impact the reimbursement for interpretive services and report preparation for both pathologists and qualified doctoral scientists
- Educate payers (Medicare, private payers and laboratory benefit managers) about the complexities of molecular testing and the intricacies involved in the analysis, interpretation, and reporting of results

Source: ClearView Analysis.