LAB TREND REPORT 2024

from Avalon Healthcare Solutions

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FROM THE DESK OF BILL KERR, MD

CEO, Avalon

Avalon is pleased to offer its fourth annual Lab Trend Report. The 2024 Avalon Lab Trend Report demonstrates how clinical laboratory testing is changing in the face of technological advancements and shifting healthcare needs. This report is made possible through our work with health plans across the country to manage their lab benefits and derive lab insights across 39+ million lives.

Improving clinical outcomes is dependent on appropriate lab testing, and this past year was no exception. At a time when increasing health care costs are more top of mind than ever, Avalon is able to capture, digitize, and analyze lab results in real-time to realize earlier disease detection, ensure appropriate treatment protocols, and cost-efficiency.

In this report, you will find statistics and analyses that will offer insight into lab testing trends, both the good news and the challenges that must be addressed. As part of the report, we share the typical routine testing activity and the increased reliance on genetic testing to predict disease conditions. One of the more challenging dynamics of the lab testing landscape are emerging trends. This report includes an entire section on emerging trends, including an update on last year's report on two innovations: multicancer early detection (MCED) tests and polygenic risks scores (PRS).

We also address the new and significant uptick in the use of biomarkers that serve as a predictor of disease risk. Biomarkers are measurable quantities derived from an objective assessment that are associated with a clinical feature, like a disease. Quite recently, clinical and direct-to-consumer tests have been developed that measure biomarkers to assess the risk of an individual developing a disease. Such risk scores are most often developed by measuring many biomarkers (for example, genetic sequences) in many patients and correlating them with specific disease outcomes, for the purpose of creating a mathematical algorithm that associates the likelihood of the disease with the results of the tests. This is an exciting but decidedly challenging arena that Avalon is focused on to make sure health plans are covering tests that deliver clinical utility.

Finally, we note that the FDA recently released a final rule to regulate lab-developed tests (LDTs), after many years of allowing mostly academic medical centers to institute their own oversight protocols. LDTs are diagnostic tests that are developed, validated, and performed in-house by individual laboratories. Some LDTs are routine tests, such as opioid testing for addiction medicine services, to more complex molecular and genetic tests for cancer, heart disease, and rare and infectious diseases. LDTs are typically at the forefront of lab medicine research, providing innovative, breakthrough tests and technologies. LDTs are critical in providing timely patient access to accurate and high-quality testing for many conditions for which no commercial tests exist, or where an existing FDA-approved commercial test does not meet current clinical needs. Overall, the thousands of LDTs performed at U.S. laboratories provide physicians with important clinical information to diagnose and treat patients, and these tests are essential to the practice of all areas of medicine.

In this report, you will find statistics and analyses that will offer insight into lab testing trends, both the good news and the challenges that must be addressed.

With the explosive growth of LDTs, the rise and fall of Theranos, and other highly publicized laboratory failures, there is an ongoing debate about the best way to regulate LDTs. The FDA is concerned that LDTs are being performed on more people than ever intended and that appropriate guardrails are not in place to protect the public. On April 29, 2024, the FDA released a final rule that will allow the FDA to regulate LDTs as medical devices. The rule will subject all in vitro diagnostics (IVDs) to FDA review, even those developed within a single laboratory. The FDA will begin to oversee LDTs within one year of the final rule's publication in the Federal Register, which was May 6, 2024.

Avalon recognizes that academic pathologists are concerned about the FDA's push to regulate LDTs. Indeed, the FDA's push to regulate LDTs would disrupt a longstanding practice of nearly all clinical laboratories in the country. Accordingly, there is significant pushback about the rule, and it is expected to be challenged in the courts now that it is finalized. As With any major change in the lab testing ecosystem, Avalon is monitoring this evolving narrative very closely.

These emerging lab trends are particularly challenging to navigate. With the help of Avalon's Clinical Advisory Board, we apply our experience in pathology and laboratory medicine to laboratory benefit management problems and solutions. In the future, we expect many new advances in molecular diagnostics and the use of artificial intelligence in laboratory medicine.

In future reports, we expect to further explore next-generation sequencing (NGS). NGS is a lab methodology that describes a whole host of different clinical tests that interrogate the human genome. NGS promises to revolutionize several areas of laboratory medicine, including those responsible for prenatal care, oncology, and genetic assessments. Particularly in the costly arena of oncology, NGS poses concerns. For example, it is unclear what the optimal size of a cancer panel should be that attempts to evaluate which, if any, causative genes may be mutated in a cancer specimen. The technology exists to sequence essentially all of the genes in any cancer specimen, but such whole-genome tests are extremely expensive and often generate extraneous and uninterpretable information. We are also cognizant that liquid biopsies are becoming more popular, a fast process of determining whether fragments of DNA indicate mutations related to cancer, but there are many unanswered questions about the overall clinical utility of the approach. As is the case in many areas of scientific inquiry, more research here is needed.

Once again, we are pleased to share our insights with you in our latest lab trend report. We appreciate your interest and look forward to your feedback. ■

EXECUTIVE SUMMARY

Lab testing is one of the many rapidly evolving areas of health care, but it is an area that receives less attention than it deserves. About 14 billion clinical lab tests are performed annually in the U.S., making them the most utilized medical benefit. Routine tests contribute to 90% of the utilization of these tests as well as ~70% of downstream clinical decisions affecting further diagnostic testing, medication use, and hospitalizations.

With great power comes great responsibility. Avalon Healthcare Solutions is dedicated to managing the breadth and depth of lab testing. In no small part, Avalon exists to address the evidence that shows a remarkable amount of both overutilization and underutilization of lab tests in the United States.

This report will show that more than 30% of lab tests conducted in the U.S. represent avoidable waste, while another 30% of patients are not receiving the testing they genuinely need. In this 2024 Lab Trend Report, we report on the lab testing landscape, statistics on 2023 lab trends, an explanation of what it all means to stakeholders, and what we can expect from the emerging technologies in the lab testing arena. In this report, we include the following:

Lab Testing Landscape - a complete introduction to routine and genetic testing, including the top 5 tests in spend and utilization in each area.

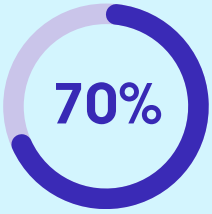
- Top routine tests that are common to the outpatient setting were almost the same for both spend and utilization: CPT 88305 (Level IV - Surgical pathology, gross and microscopic examination), CPT 80053 (Basic & Comprehensive Metabolic Panel), CPT 80061 (Lipid Panel), and CPT 85025 (Complete Automated Blood Count (CBC) with automated differential White Blood Cell (WBC) count).
- Top genetic test (spend) was CPT code 81420, which is the code for Fetal Chromosomal Aneuploidy, which is consistent with analysis for extra or incomplete chromosomes. The spend associated with this code was $2.62 per 100 members per year. Oncology and other tests for evaluating fetal health were also in the top 5 genetic tests by spend.

Snapshot of 2023 Lab Testing Data – a review of the data Avalon collected in 2023, concluding that the overall spend on routine lab tests was $175 per member per year, and that the amount of spend on the top 5 genetic tests increased in 2023 as compared to 2022.

- For routine tests, the 2023 spend data shows a 13% decrease from $200 PMPY in 2022. This decreased spend is associated in large part with decreased spend on COVID-related testing.
- In 2023, the overall utilization of routine lab tests was 6.39 tests per member per year (PMPY). This analysis was based on utilization of over 100 million tests among approximately 16 million members. This utilization represents a 6% decrease from 6.80 tests PMPY in 2022.
- For genetic tests in 2023, the overall spend was $13.42 per member per year (PMPY). This spend represents an 8% increase from $12.47 PMPY in 2022, likely due to both the increasing costs of

genetic tests as well as the increasing use of genetic testing. Given the fact that the growth in spend (8%) was greater than the growth in utilization (5%), it is likely that the increased cost of testing played a larger role here as well.

Annually, about 14 billion clinical lab tests are performed in the U.S., making them the most utilized medical benefit.



Laboratory testing affects ~70% of downstream treatment decisions.

More than 30% of clinical lab tests conducted in the U.S. are inappropriate or unnecessary.

2023 Lab Trends – our analysis of how to address the growth and costs of routine and genetic testing, including insights into why the site of lab testing and thoughtful prior authorization processes matter so much.

- Place of service matters: When comparing lab charges for common routine tests, the outpatient services sites (generally hospital labs) and physician office settings were considerably more expensive than independent labs. The price differential has been increasing over time - hospital outpatient lab services rose from 9 to 46% from 2022 to 2023.
- Prior authorization processes: The top five tests determined to be noncompliant with prior authorization processes represent a combination of discriminate, non-well-defined codes often used with genetic test orders. For example, the CPT code 81479, the number one code in terms of noncompliant units, represents an assortment of laboratory derived tests without more specific description, making such tests difficult to document and even more challenging to manage.

Averted Costs and Lab Value Management – this section includes a case study on averted costs as well as two examples of how Avalon is combining lab values with the appropriate action steps in patient care to create opportunities for delaying disease progression while reducing costs.

Emerging Trends – a peek into the future of clinical laboratory testing. We explore a few emerging issues including two issues we addressed in the 2023 Lab Trend Report: multicancer early detection (MCED) tests and polygenic risks scores (PRS). We also review advances in blood biomarker testing and the FDA's plan to regulate lab-developed tests (LDTs).

In short, this report shows how lab testing is an essential part of the patient journey. Avalon demonstrates how to interpret the data on routine and genetic testing and what to do about it. Despite its relatively small piece of the health care system cost pie, lab testing is the doorway to better health and cost savings. Thank you for reading and sharing the Avalon 2024 Lab Trend Report.

LAB TESTING LANDSCAPE

Introduction

Laboratory testing is an integral part of modern medicine. Multiple types of savings – measured in lives, costs, and time – are attributable to clinical laboratory tests enabling early detection and prevention of disease. With a growing geriatric population, the rising prevalence of chronic diseases that require diagnostic monitoring, and a higher market penetration of new and technologically advanced diagnostic techniques, lab tests are only becoming more consequential to the healthcare system.

The following are a few remarkable statistics to illustrate the importance of lab testing:

- Lab testing is one of the highest volume medical activities in the U.S., with more than 14 billion tests performed each year.[1]
- The clinical laboratory testing market was valued at $46 billion in 2022 and is expected to grow 6.5% per year from 2024-2030.[2]
- A meta-analysis of studies published from 1997 to 2012 estimated the rate of inappropriate testing, including overutilization (i.e., avoidable waste), at 20.6% and the rate of underutilization at 44.8%.[3]
- Despite laboratory testing accounting for only a small fraction (3-4%) of healthcare spending,[4] it nonetheless matters a great deal to the downstream health care services that testing leads to or prevents. The costs of these post-test activities – prescriptions, imaging, surgeries, hospital stays – amount to numbers that dwarf the cost of laboratory testing. And yet, laboratory testing affects ~70% of all downstream treatment and management decisions.[5]

With these factors in mind, it is obvious why there is such a need to ensure that patients receive the right test at the right time for the right indication. Avalon Healthcare Solutions is dedicated to helping health plans manage these advanced diagnostic technologies to improve the health care of their members and improve the efficiency of the overall system.

The clinical laboratory testing market was valued $46 billion in 2022 and is expected to grow 6.5% per year from 2024-2030.

Introduction to Routine Testing

Routine tests are defined as tests that evaluate health metrics and can be repeated over time to monitor and compare the changing health condition of an individual. Routine tests make up ~90% of all lab testing volume.

The most common types of routine blood tests for annual checkup include a Complete Automated Blood Count (CBC), which measures the number and types of blood cells in the body, and a Basic Metabolic Panel (BMP), which measures levels of glucose, electrolytes, and other blood chemistries.[6]

Blood tests are among the most common types of diagnostic tests. The yield on routine testing can be wide-ranging, as outlined below, and this yield is achieved by analyses from a simple blood draw. Furthermore, the convenience of routine testing as an outpatient procedure with minimal to no risk facilitates the frequent use of routine testing. In fact, even though there is a CPT code for venipuncture (CPT code 36415 for all routine venipunctures, not requiring the skill of a physician, for specimen collection), the test itself is often not referred to as a procedure.

Why Are Routine Lab Tests Important?

- Early detection of health issues, such as diabetes and high cholesterol, in which early diagnosis and treatment are useful.
- Preventative care and evaluation of risk factors amenable to management to alter the onset of disease and disability.

- Assessment of baseline organ function and monitoring changes over time increases the chances that such evaluation can prevent a potential problem by interventions like medications or lifestyle changes.
- Personalized healthcare is used by health care providers to gain information to develop and educate on a care plan for care management that is specific to a given individual.
- Monitoring chronic conditions to measure the effectiveness of treatment strategy and identify any changes that may necessitate a change in the management plan.

Despite these important use cases, there are several factors that contribute to less-than-optimal utilization in the outpatient care setting. In a telephone survey conducted among 600 primary care and specialist physicians across the United States, several factors were identified.[7]

- The top reasons physicians say they order unnecessary tests and procedures are concern about malpractice issues (52% consider this scenario as a major reason), just to be safe (36%), and wanting more information for reassurance (30%).
- The second-tier influences are patients' insistence (28%) and wanting to keep patients happy (23%).
- Third-tier reasons include other factors such as not having enough time with patients (13%), the fee-for-service system (5%), and new technology in their practice (5%).

What Is the Optimal Amount of Testing?

Of all the options available to laboratorians to affect positive change, test utilization management (UM) is among the most effective and universally achievable. A large meta-analysis showed that ~20% of ordered tests are unnecessary, while roughly ~45% of the time, tests that would have provided more optimal patient care were not ordered.[8] Furthermore, perhaps the term "routine," as in routine testing, serves to negate the complexity underlying the appropriate ordering of laboratory tests and thus contributes to overutilization.[9] These findings suggest the laboratory does have a responsibility to help guide the provider in ordering the right tests at the right time and in the right sequence.

Efforts to improve routine testing will be facilitated by multiple medical societies and guidelines. The American Society for Clinical Pathology and the American Society for Clinical Laboratory Science have developed practice guidelines that outline optimal use and mitigate against less-than-optimal testing. Examples include the recommendation not to repeat A1c testing in stable patients within 3 months of a previous result[10] as well as avoiding thyroid stimulating hormone (TSH) screening in annual well-visits for asymptomatic adults, regardless of age.[11]

Introduction to Genetic Testing

What Is a Genetic Test?

Genetic testing is the use of laboratory procedures to analyze chromosomes, genes, or gene products. A genetic test involves an analysis of human chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genes, and/or gene products (e.g., enzymes and other types of proteins), which is predominately used to detect heritable or somatic mutations, genotypes, or phenotypes related to disease and health. These tests are generally more complex and more expensive than routine tests and are performed less regularly. Genetic tests make up ~10% of all lab test utilization and a disproportionate ~30% of all lab spend.

There are three main types of genetic testing.[12]

- Chromosome studies examine the threadlike structures of DNA in every cell and are useful in evaluating gene sequences (deletions, additions, or misspellings) for inherited disorders.
- Gene studies examine DNA and RNA are useful in the diagnosis and monitoring of cancer.
- Gene products are biochemical studies that evaluate the presence of abnormal enzymes, other proteins, and metabolites.

Genetic testing is increasingly being used in clinical and public health practices to assist disease diagnosis, predict disease risk, and guide patient care.[13],[14] Such genetic tests are available to aid physicians in the diagnosis and therapy of many diseases.

- Monitoring treatment in patients
- Conformational diagnosis of a symptomatic individual
- Presymptomatic testing for estimating risk of developing disease
- Presymptomatic testing for diagnosing a disease that will manifest later
- Prenatal screening and diagnosis
- Newborn screening
- Preimplantation genetic diagnosis
- Carrier screening
- Forensic testing
- Paternal testing

Specifically, there are three areas highlighted below that represent major growth drivers. Payers already see claims for these indications in their lab spend and trend. We expect that these areas will continue to dominate in the near term.

- **Companion Diagnostics (CDx).** CDx allow doctors and patients to better understand if therapies will respond for specific patients. The growth in CDx is often closely linked to "precision medicine" or "personalized medicine."
- **Non-Invasive Prenatal Testing (NIPT).** For a long time, the need to understand the health of developing fetuses without engaging in invasive testing has been a focus area. The increasing focus on liquid biopsies and new biomarkers is fueling the demand for NIPT.
- **Direct-to-Consumer Testing.** As patients become more active in understanding genetic variations, progeny, and legacy – the market for direct-to-consumer (DTC) testing continues to grow.[15]

The increase in genetic test availability and use in the US is not surprising, given ongoing and recent initiatives. The completion of the Human Genome Project (HGP) in 2003 and the resultant increase in data and information on human genetics has led to the development of thousands of genetic tests.[16] Precision medicine has transformed over the last two decades to support disease diagnosis and screening, predict disease risk, inform patient drug responsiveness, and understand individual ancestry. In January 2015, President Barack Obama launched a Precision Medicine Initiative investing $215 million dollars to support research, development, and innovation of precision medicine. Indeed, in 2022, President Biden re-launched the Cancer Moonshot initiative because of recent progress in cancer diagnostics and therapeutics.[17] The Healthy People 2030 initiative focuses on increasing the proportion of women with a family history of breast and/or ovarian cancer who receive genetic counseling.[18]

Payers are now faced with an increasing number of requests to cover genetic testing, to determine whether it is appropriate under the circumstances amid a rapidly changing landscape. Today, tests are created faster than new codes can be assigned to identify them, so a wide range of genetic testing is lumped under one nondescript Current Procedural Terminology (CPT) code. While some genetic tests can be ordered using highly specific codes that are applicable only to a single gene or analyte, many tests are handled under the catch-all CPT 81479 code. There are more than 40,000 different tests associated with that single code.[19]

40,000 DIFFERENT TESTS

Many genetic tests are handled under the catch-all CPT 81479 code. There are more than 40,000 different tests associated with that single code.[19]

How Big Is the Market?

According to a November 2022 analysis of trends in the availability of genetic tests in the United States over the last decade, a total of 175,000 genetic tests are currently available in the U.S., including updated versions of previously existing tests.[20] Of note, 10 new tests are introduced every day.

The Genetic Testing Registry (GTR), a National Library of Medicine initiative along with the National Center for Biotechnology Information, now lists 73,972 tests, 24,777 conditions, 18,725 genes, and 453 labs.[21] In the U.S., 200 laboratories performed 37,124 different clinical tests on the interactive database. Of note, more than 99% of these tests performed were for clinical purposes.

There is a strong concentration of genetic test development among a few labs. Over the past 10 years, a total of 51,803 new genetic tests were made available in the U.S., an increase from the 607 new genetic tests in 2012.

- 93% of these (47,929 tests) were developed by 31 CLIA-certified laboratories.
- 81% (41,666 tests) were developed by only 10 CLIA-certified laboratories across the U.S.
- 62% (32,185 tests) registered to the GTR in the U.S. are diagnostic. Diagnosis is the largest genetic test purpose category on the registry. After diagnosis, 5646 (10.9%) new genetic tests are for risk assessment, 5410 (10.4%) new genetic tests are for pre-symptomatic testing, and 5370 (10.4%) are for screening.

The overall spend for genetic testing reached $8.1B in 2021 and $8.91B in 2022. This figure is expected to go to $19.8B in 2032, representing a CAGR of 10.5%. Cancer screening leads the growth.[22]

What Are the Drivers of Growth in Utilization and Spend and Trend?

Drivers of genetic test development and subsequent spend include the following:

- Increase in incidences and prevalence of genetic disorders and chronic disease
- Growth in awareness and acceptance of personalized medicines by providers
- Growth in awareness and acceptance of personalized medicines by patients
- Advancements in genetic testing techniques

Challenges to these drivers exist as well. These factors are expected to restrict market growth during the forecast period.[23],[24]

- Standardization concerns of genetic testing-based diagnostics
- Stringent regulatory requirements for product approvals
- Dearth of experienced clinical prescribers
- Dearth of trained lab professionals

Routine Testing - Top 5 Spend

Out of the 100,105,546 routine lab tests that Avalon managed in 2023, we identified the top five routine lab tests across all business lines in terms of per member per year (PMPY) spend (Table 1). Of note, these figures represent the allowed amount versus the billed amount for lab spend, as tests are screened out from the system using the Avalon Routine Test Management program, such that the spend for allowed testing is less than the spend for billed testing.

The top routine test in terms of spend was CPT 88305, which is the code for Level IV surgical pathology, gross and microscopic examination, at $15.00 PMPY.

- In general, routine tests are blood tests designed to evaluate the function of multiple organ systems, allowing for early detection of disease and monitoring the management plan for chronic diseases.
- Yet skin biopsy shares several properties with a routine test, as a skin biopsy is performed to allow for early detection of disease (skin cancer) as well as evaluation and diagnosis of pre-cancerous lesions.

The remainder of the top 5 routine tests by spend in

2023 represent common tests utilized in the care and management of patients in the outpatient setting and likely ordered during the annual wellness visits.

- A new addition to the list is the CPT code 85025, which is the code for Complete Automated Blood Count (CBC) analysis.
- The test that dropped off the list in 2022 is the special pandemic code U0003, which is the code for PCR/high-throughput screening tests associated with COVID-19 testing. This code was introduced in 2020 and quickly appeared in the top 5 for lab spend, as it was number 2 on the list of the top 5 routine tests by lab spend in 2022. Consistent with this finding, the data on COVID testing overall in 2023 dropped 58% from 2022 levels.
- Spend on the top 5 routine tests in 2023 decreased as compared to 2022. This finding is consistent with the decrease in overall spend PMPY noted in 2023 versus 2022.

Table 1. Routine Test Management Top 5 Spend

CPT Code	Test	PMPY Spend	Description
88305	Level IV - Surgical pathology, gross and microscopic examination	$15.00	Surgical pathology involves the gross and microscopic examination by surgical (e.g., dermatologists) and non-surgical providers (e.g., pathologists) of surgical or biopsy specimens
80053	Basic & Comprehensive Metabolic Panel	$7.49	Glucose, urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), chloride (CL), carbon dioxide (CO2), anion gap, calcium, total protein, albumin, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, GFR (African American), GFR (Others)
80061	Lipid Panel	$4.87	Total cholesterol, serum (82465), lipoprotein, direct measurement, HDL (83718), triglycerides (84478)
85025	Complete Automated Blood Count (CBC)	$4.33	White blood cells or "diff" in which the following leukocytes are differentiated: neutrophils or granulocytes, lymphocytes, monocytes, eosinophils, and basophils
80050	Complete Health Panel	$4.19	Comprehensive metabolic panel (80053), blood count, thyroid stimulating hormone (TSH) (84443), and complete automated blood count (CBC) (85025)

Reference. *Avalon data on file*

As compared to the top 5 routine tests by utilization, the results of the top 5 routine test by spend demonstrated a similar list of tests common to the outpatient setting: CPT 88305, CPT 80053, CPT 80061, and CPT 85025 are present on both top 5 lists. This scenario is most likely due to the large volume of test ordering for the relatively inexpensive CPT 80053, CPT 80061, and CPT 85025 codes as well as the high price per code associated with pathology testing CPT 88305.

Takeaways from our analysis of spending on routine testing:

- Consolidation of hospital and physician practice groups increases health plan medical spend due to new rates for the same services. A lab test's price can vary dramatically (up to severalfold differences) depending on where it is performed. Site-neutral payment legislation may reduce the disparity among sites of service.
- COVID testing, prominent on the top 5 routine tests by spend in 2022, does not appear in the top 5 for 2023.
- The results demonstrated a similar list of routine tests for both spend and utilization common to the outpatient setting: CPT 88305, CPT 80053, CPT 80061, and CPT 85025 are on both spend and utilization top 5 lists.
- CPT 80050 represents several tests not congruent with each other and may represent panel stuffing. A Complete Health Panel, CPT 80050, is not covered by Medicare, primarily because of the diversity of test components. CMS states that no single diagnosis code would merit the diverse testing such a panel entails, and therefore the tests in this panel should be ordered individually, with appropriate medical necessity documentation.

How Can Avalon Help?

Avalon contracts with independent laboratories, creating a broad network that supports client health plans. Excess laboratory spend can be avoided through point-of-service optimization. Programs that drive utilization to independent labs can achieve marked cost savings in an administrative manner that is a natural combination with other measures to improve utilization overall.

- Most patients and consumers are not aware of this and their potential savings.
- Payers should pursue programs that drive utilization to high quality, independent labs which can achieve marked cost savings in an administrative manner that is a natural combination with other measures to improve utilization and spend overall.

Routine Testing - Top 5 Utilization

Out of the 100,105,546 routine lab tests that Avalon managed in 2023, we identified the top five routine lab tests across all business lines in terms of per member per year (PMPY) utilization (Table 2). Of note, these figures represent allowed versus billed lab utilization, as tests are screened out from the system using the Avalon Routine Test Management automated policy enforcement application, such that allowed testing is less than billed testing.

The top routine test in terms of utilization was CPT 80053, which is the code for the Basic & Comprehensive Metabolic Panel, at 2658 units /10,000 members.

- The Basic & Comprehensive Metabolic Panel consists of over a dozen blood tests, serving as an initial broad medical screening tool and providing information on the management of several chronic diseases.
- Routine chemistry tests, such as those depicted by this code, represent the evaluation of blood analytes and are generally associated with the

highest volume of routine testing in clinical laboratories.

The remainder of the top 5 routine tests by utilization in 2023 represent common tests utilized in the care and management of patients in the outpatient setting.

- There are no new changes to the top 5 routine tests in 2023 as compared to 2022.
- Utilization of the top 5 routine tests decreased in 2023 as compared to 2022, and, this finding is consistent with a decrease in overall utilization PMPY noted in 2023 versus 2022.

Table 2. Routine Test Management Utilization

CPT Code	Test	Number of Units /10,000 Members	Description
80053	Basic & Comprehensive Metabolic Panel	2658	Glucose, urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), chloride (CL), carbon dioxide (CO2), anion gap, calcium, total protein, albumin, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, GFR (African American), GFR (Others)
85025	Complete Automated Blood Count (CBC)	2478	White blood cells or "diff" in which the following leukocytes are differentiated: neutrophils or granulocytes, lymphocytes, monocytes, eosinophils, and basophils
80061	Lipid Panel	2405	Total cholesterol, serum (82465), lipoprotein, direct measurement, HDL (83718), triglycerides (84478)
88305	Level IV-Surgical pathology, gross and microscopic examination	1592	Surgical pathology involves the gross and microscopic examination by surgical (e.g., dermatologists) and non-surgical providers (e.g., pathologists) of surgical or biopsy specimens
83036	Hemoglobin; Glycosylated (A1c)	1575	Glycosylated hemoglobin A1c, usually determined by ion-exchange affinity chromatography, immunoassay or agar gel electrophoresis

Reference. *Avalon data on file*

As compared to the top 5 routine tests by spend, the results of the top 5 routine tests by utilization demonstrated a similar list of tests common to the outpatient setting: CPT 88305, CPT 80053, CPT 80061, and CPT 85025 are present on both top 5 lists. This scenario is most likely due to the large volume of test ordering for the relatively inexpensive CPT 80053, CPT 80061, and CPT 85025 codes as well as the high price per code associated with pathology testing CPT 88305.

Takeaways from our analysis of the lab testing utilization:

- The top 4 tests represent codes for assessing and monitoring a variety of chronic illnesses, often done during annual wellness checks.
- The utilization of the CPT 88305 code is not likely generated through primary care and more likely represents a common outpatient procedure for the evaluation of cancer, including skin biopsies, prostate biopsies, and bone marrow biopsies.
- The results demonstrated a similar list of routine tests common to the outpatient setting: CPT 88305, CPT 80053, CPT 80061, and CPT 85025 are on both utilization and spend top 5 lists.
- While the Basic & Comprehensive Metabolic Panel test leads as the number one test, all the blood chemistries provided are well aligned and congruent with the broad evaluation of chronic diseases.

How Can Avalon Help?

Education on the roles and goals of testing as well as associated program integrity can help identify avoidable waste and ensure optimal testing.

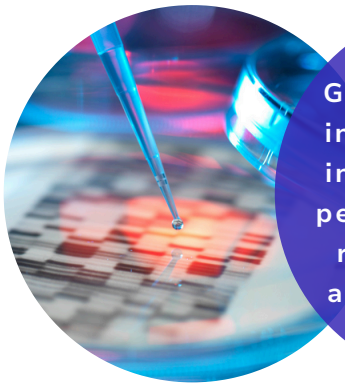
- Laboratory testing itself accounts for only a tiny fraction of healthcare spending. The major costs come from follow-up clinical care plans and activities that stem from such testing, including false positives as well as false negative results. These follow-up clinical care processes include medication prescriptions, subsequent office visits, radiological imaging, surgeries, and hospital stays.
- Removing low-quality, wasteful testing upstream can decrease these larger downstream costs.

Genetic Testing - Top 5 Spend

Of the ~500,000 genetic lab tests that Avalon managed in 2023, we identified the top five genetic lab tests across all business lines in terms of per 100 members per year spend (Table 3). Of note, these figures represent the allowed amount versus the billed amount for lab spend, as tests are screened out from the system using the Avalon Genetic Test Management program, such that the spend for allowed testing is less than the spend for billed testing.

Genetic testing is increasingly being used in clinical care in line with the movement to more personalized, precision health risk assessment and intervention. Genetic tests include tests that evaluate fetal/child health, such as prenatal screening and diagnosis of newborns, and information on disease diagnosis, prognosis, and optimized treatment management.

- The top genetic test in terms of spend was CPT code 81420, which is the code for Fetal Chromosomal Aneuploidy, which is consistent with analysis for extra or incomplete chromosomes. The spend associated with this code was $2.62 per 100 members per year.
- Other tests for evaluating fetal health, CPT code 81220 and CPT code 81416, were also noted in the top 5 genetic tests by spend.
- Oncology tests also featured prominently on the top 5 list. CPT code 81519 represents a test designed to provide personalized genomic insights for early-stage breast cancer in terms of the likelihood of benefit from chemotherapy and risk of distant recurrence. CPT code 81162 represents a test designed to look at inherited cancer risks for one or more cancers, including breast and ovarian cancer, in patients that will affect future prognosis and treatment monitoring strategies.
- All tests present in the top 5 genetic tests by spend in 2023 also appeared on the list for 2022.
- Spend on the top 5 genetic tests increased in 2023 compared to 2022. This finding is consistent with the increase in overall spend for genetic tests per 100 members per month noted in 2023 versus 2022.



Genetic testing is increasingly used in clinical care to personalize health risk assessment and intervention.

Table 3. Genetic Test Management Spend

CPT Code	Utilization Rank	Spend /100 Members	Description
81420	Fetal Chromosomal Aneuploidy	$2.62	Fetal Chromosomal Aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21.
81220	CFTR Gene Com Variants	$0.94	CFTR (cystic fibrosis transmembrane conductance regulator) gene analysis; common variants
81519	Oncology Breast mRNA	$0.80	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
81162	BRCA1&2 Gen Full Seq Dup/Del	$0.66	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/ deletion analysis (i.e., detection of large gene rearrangements)
81416	Exome Sequence Analysis	$0.50	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator/ exome (e.g., parents, siblings)

Reference. *Avalon data on file*

Description. *The top 5 genetic tests by spend consist of two groups of clinical care interest: fetal/child health and oncology diagnosis and management. The list of top 5 genetic tests by spend in 2023 is similar to that seen in 2022.*

The results on the top 5 genetic tests by spend demonstrated some strong similarity to the list of genetic tests common to the top 5 genetic tests utilization list. Both lists had frequent mentions of genetic tests for fetal/child health: CPT codes 81420 and CPT 81220 appear on the spend and utilization lists. Oncology tests appeared on the spend list, but not the utilization list, consistent with the high price associated with these tests intended to help with diagnosis, prognosis, and treatment monitoring opportunities among cancer patients.

Takeaways for the top 5 spend for genetic tests include:

- The spend results demonstrated a similar list of genetic tests common to the outpatient setting as described in the genetic test utilization section above. CPT 81420 and CPT 81220 are on both lists.
- Fetal/child health and oncology diagnosis and prognosis tests dominate the top 5 genetic tests by spend.
- The unlisted molecular pathology code represents a grab bag test code, described as an unlisted molecular pathology procedure and mentioned in the utilization section, ranked eight on the spend list.
- The 2023 highest-ranking genetic tests by spend was similar to that of 2022.
- Overall spend on genetic testing increased from 2022 and is expected to continue to do so going forward, as physician and patient interest in personalized, precision medicine grows.

How Can Avalon Help?

Avalon contracts with high-quality independent laboratories, creating a broad network that supports client health plans. Preferred networks can be helpful in optimizing costs for needed tests with proven benefits as determined by guidelines and test performance.

Excess laboratory spend can be avoided through point-of-service optimization. Programs that drive spend and utilization to independent high-quality labs can achieve marked cost savings in an administrative manner that is a natural combination with other measures to improve utilization overall. Data sharing between Avalon and health plans can allow for better quality assessment, given the opportunity to look for overutilization as well as underutilization of testing.

Genetic Testing - Top 5 Utilization

Of the ~500,000 genetic lab tests that Avalon managed in 2023, we identified the top five genetic lab tests by utilization across all business lines in terms of per 10,000 members per year (Table 4). Of note, these figures represent allowed versus billed lab utilization, as tests are screened out from the system using the Avalon Genetic Test Management program, such that allowed testing is less than billed testing.

Genetic testing is increasingly being used in clinical care in line with the movement to more personalized, precision health risk assessment and intervention. Genetic tests include tests that evaluate fetal/child health, such as prenatal screening and diagnosis of newborns, and information on disease diagnosis, prognosis, and optimized treatment management.

- The top genetic test in terms of utilization was CPT code 81420, which is the code for Fetal Chromosomal Aneuploidy. The utilization associated with this code was 54.93 units per 10,000 members per year.
- Other tests for evaluating fetal health, CPT code 81220, CPT code 81329, and CPT code 88271 were also noted in the top 5 genetic tests by utilization.
- One test used for tissue typing was included in the top 5 list. CPT code 81374 represents a test designed to provide information that may be helpful for facilitating transplantation, identifying certain diseases associated with rheumatological disorders, and identifying pharmacogenetic patterns to guide medication use.
- CPT code 81479 (unlisted molecular pathology) and CPT code 81241 (F5 gene) were included among the top 5 genetic tests by utilization in 2022 but did not make the list in 2023.
- Utilization of the top 5 genetic tests in 2023 was increased as compared to 2022. This finding is consistent with the increase in overall genetic test utilization per 10,000 members per year noted in 2023 versus 2022.

Utilization of the top 5 genetic tests in 2023 was increased as compared to 2022. This finding is consistent with the increase in overall genetic test utilization.

Table 4. Genetic Test Management Utilization

CPT Code	Utilization Rank	Number of Units /10,000 Members	Description
81420	Fetal Chromosomal Aneuploidy	54.93	Fetal Chromosomal Aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21.
81220	CFTR Gene Com Variants	26.21	CFTR (cystic fibrosis transmembrane conductance regulator) gene analysis; common variants
81329	SMN1 Gene Dos/Deletion Alys	15.44	SMN1 (survival of motor neuron 1, telomeric) gene analysis: dosage/deletion analysis, includes SMN2 (survival of motor neuron 2, centromeric) analysis if performed
81374	HLA Typing 1 Antigen	10.62	Human leukocyte antigen genes, called HLA, for one Class I antigen equivalent
88271	Cytogenetics DNA Probe	9.41	Molecular cytogenetic test using a DNA probe method,'such as FISH, fluorescence in situ hybridization, to test cells for genetic abnormalities

Reference. *Avalon data on file*

Legend. *The top 5 genetic tests by utilization consist of two groups of clinical care interest: fetal/child health and transplant/rheumatology diagnosis and management.*

The results on the top 5 genetic tests by utilization demonstrated some strong similarity to the list of genetic tests common to the top 5 genetic test spend list. Both lists frequently mentioned genetic tests for fetal/child health: CPT codes 81420 and CPT 81220 appear on the spend and utilization lists. Oncology tests appeared on the spend list, but not the utilization list, consistent with the high price associated with these tests intended to help with diagnosis, prognosis, and treatment monitoring opportunities among cancer patients.

The takeaways on utilization for the top 5 genetic tests include:

- The top 5 genetic tests by utilization showed a similar list as described in the genetic test spend section above: CPT 81420 and CPT 81220 are on both lists.
- Fetal/child health assessment tests dominated the top 5 genetic tests by spend and utilization. The spend list also included two oncology tests, while the utilization list also included a test for histocompatibility.
- One major change in 2023 was that the unlisted molecular pathology code CPT code 81479, representing a grab bag test code and described as an unlisted molecular pathology procedure, dropped out of the top 5 genetic tests by utilization in 2023 versus 2022 and was ranked 12th on the spend list in 2023.
- Overall utilization of genetic testing increased in 2023 from 2022 and is expected to continue to do so going forward, as physician and patient interest in personalized, precision medicine grows.

How Can Avalon Help?

- Avalon contracts with high-quality independent laboratories, creating a broad network that supports client health plans. Preferred networks can be helpful in optimizing costs for needed tests with proven benefits as determined by guidelines and test performance.
- Programs that drive spend and utilization to independent labs can achieve marked cost savings in an administrative manner, which is a natural combination with other measures to improve utilization overall.
- Excess laboratory utilization can be avoided through point-of-service optimization. This finding is associated with improved surveillance of CPT code 81479.
- Data sharing between Avalon and health plans can allow for better quality assessment, as it allows for identifying overuse and underuse of testing.

SNAPSHOT OF 2023 LAB TESTING DATA AND LAB TRENDS

Routine Testing - Landscape Spend and Utilization

In 2023, the overall spend on routine lab tests was $175 per member per year (PMPY). This analysis was based on a spend of $2.7 billion among approximately 16 million members.

- This spend figure represents a 13% decrease from $200 PMPY in 2022 (see Figure 1 below).
- We believe that this overall decrease in overall spend over time is associated with three factors in particular:
  - Decreased COVID-related testing
  - Muted recovery after the pandemic with return to office visits
  - Active Avalon Routine Testing program management affecting spend/utilization trends

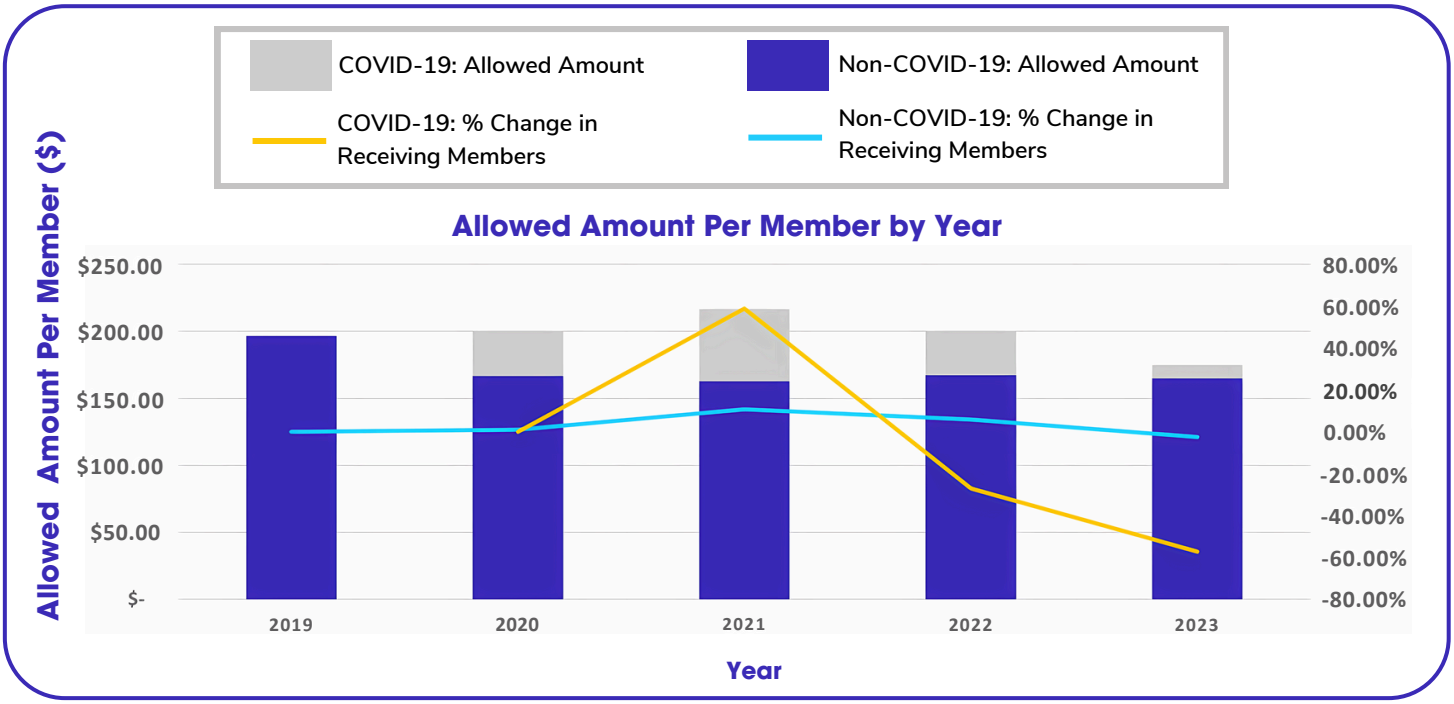
Among members who had one or more routine tests in 2023, the data demonstrate skewing towards high spend members, as the mean spend ($273) isgreater than the median spend ($114) here.

In 2023, the overall utilization of routine lab tests was 6.39 tests per member per year (PMPY). This analysis was based on utilization of over 100 million tests among approximately 16 million members.

- This utilization represents a 6% decrease from 6.80 tests PMPY in 2022.
- The percent decrease in spend (13%) was greater than the percent decrease in utilization (6%). This finding suggests that mix was decreased, which may have been associated with a shift from more expensive to less expensive testing, as well as effects from Avalon controlled spend/trend through its active program management.

Among members who had one or more routine tests in 2023, the mean number of tests per member (9) was greater than the median number of tests per member (6), suggesting the skewing of test use towards high users.

Figure 1. Trends in Spend and Trend for Routine Testing 2019 – 2023 Showed NON-COVID and COVID Related Testing



Reference. *Avalon data on file*
Description. *Non-COVID-related spending is down slightly from 2022 and significantly from pre-pandemic year 2019, and COVID-related spending continues to markedly decrease since 2021.*

Routine Testing - Spend and Utilization Trends

Routine Testing - Trend in Spend

We analyzed spend for routine tests among Avalon clients across all books of business for this analysis.

In 2023, the overall spend on lab tests was $175 per member per year (PMPY), a 13% decrease from $200 PMPY in 2022. This analysis was based on a spend of $2.7 billion among approximately 16 million members.

This decreased spend is mostly related to decreased spend on COVID-related testing (see Figure 1 above).

- Overall spend decreased by 19% from $217 in 2021, which was the peak year in this analysis. Overall trend in lab spend for routine testing in this analysis has been strongly driven by the amount of COVID-related testing.
- Non-COVID-related spend decreased slightly from 2022 and decreased 16% from $197 during pre-pandemic 2019, which was the peak year in this analysis. Non-COVID-related testing has been flat since 2020, associated with the muted recovery after the pandemic regarding return to office visits and active management by Avalon through our services.
- COVID-related spend decreased from a peak of $54 PMPY in 2021 that accounted for 25% ($54/$217) of routine test spend, to $10 PMPY in 2022 that accounted for only 6% ($10/$175) of routine test spend. COVID testing rules remain in place, and testing has moved largely from nucleic acid amplification tests such as polymerase chain reaction (PCR) assays performed in the clinical laboratory to rapid antigen tests (RATS), which are generally self-testing done as at-home tests.

We note from the literature on routine testing that the trend in spend is expected to increase from 2-5% per year in the next 5-8 years.[25],[26]

Routine Testing – Trend in Utilization

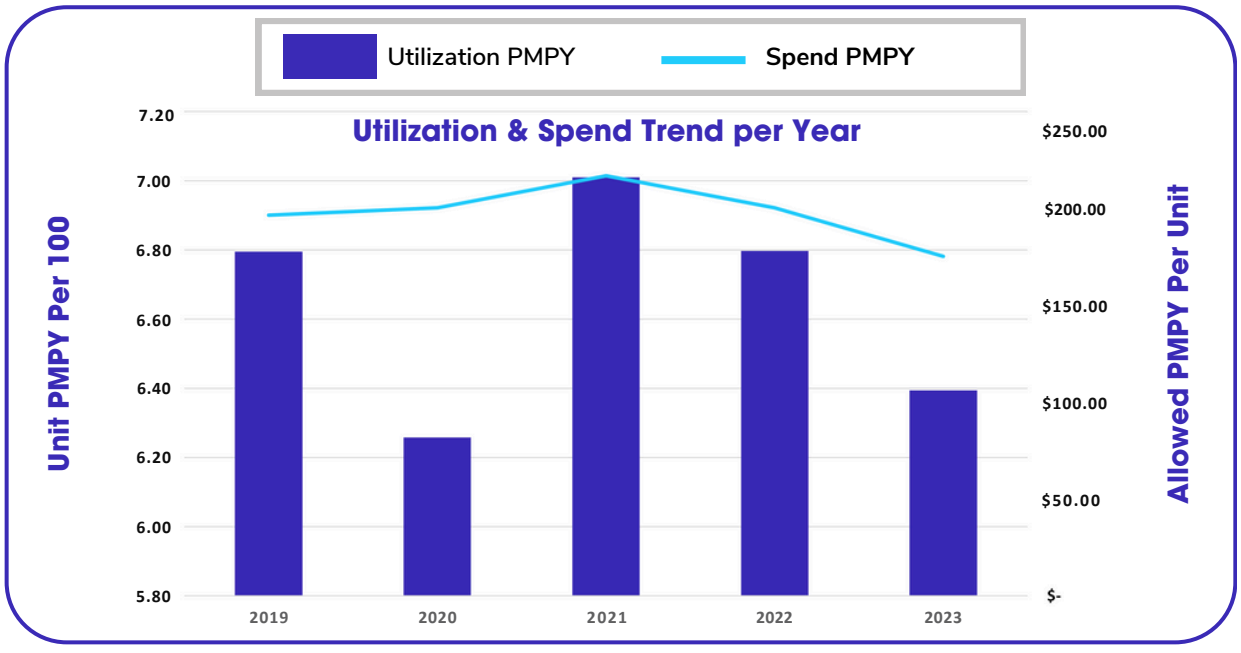
In 2023, the overall utilization of routine lab tests was 6.39 tests per member per year (PMPY), a 6% decrease from 6.80 tests PMPY in 2022 (see Figure 2 below). This analysis was based on utilization of over 100 million tests among ~16 million members.

- This utilization represents a 6% decrease from 6.80 tests PMPY in 2022.
- Overall utilization decreased by 9% from 7.01 tests in 2021, which was the peak year in this analysis.
- Non-COVID-related utilization decreased slightly from 2022 and decreased 7% from pre-pandemic 2019.
- COVID-related utilization decreased 81% from a peak of 2021. COVID testing rules remain in place, and testing has moved largely from nucleic acid amplification tests such as polymerase chain reaction (PCR) assays performed in the clinical laboratory to rapid antigen tests (RATS), which are generally self-testing done as at-home tests.

We analyzed Routine Test Management for health plans engaged with Avalon in 2023 to look for patterns of utilization among members. In this subgroup analysis of 10,208,447 members who had at least one routine CPT code procedure over the year, we measured utilization and spend figures (Table 5). We believe that this overall decrease in overall utilization over time is associated with three factors in particular:

- Decreased COVID-related testing
- Muted recovery after the pandemic with return to office visits
- Active Avalon Routine Testing program management affecting spend/utilization trends

Figure 2. Trends in Routine Testing 2019 - 2023 Show a Decrease in Spend and Utilization Noted Over Time



Reference. *Avalon data on file*

Description. *Both spend and utilization on routine testing decreased in 2023 versus 2022. Of note, peak changes in utilization and spend trend occurred from 2020 to 2021, most likely due to depressed baseline numbers in 2020 due to pandemic-related events.*

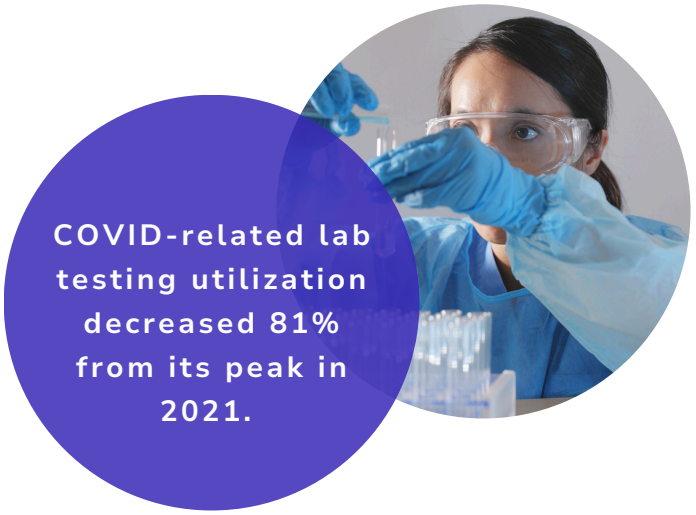
Table 5. Routine Tests Utilization and Spend Figures for 2023

Category	Utilization PMPY	Spend PMPY
Mean	9	$273
Median	6	$114
Standard Deviation	12.05	$747
Quartile 1	3	$46
Quartile 3	11	$272
Intra-quartile Range	8	$226

Reference. *Avalon data on file*

Key findings on trends in spend and utilization in routine testing:

- In 2023, the overall spend on routine lab tests was $175 per member per year (PMPY). This spend represents a 13% decrease from $200 PMPY in 2022.
- In 2023, the overall utilization of routine lab tests was 6.39 tests per member per year (PMPY). This utilization represents a 6% decrease from 6.80 tests PMPY in 2022.
- Utilization of routine tests peaked in 2019 and spend associated with routine tests peaked in 2021.
- The percent decrease in spend (13%) was greater than the percent decrease in utilization (6%). This finding suggests that the mix was decreased, which may have been associated with a shift from more expensive to less expensive testing, as well as effects from Avalon controlled spend/trend through its active program management .



Avalon Can Help Manage Routine Test Spend and Utilization

Health plans may wish to address these outliers in terms of spend and utilization, as these plans determine what tests are covered and paid for under the plan's policies. Avalon offers health plans robust evidence-based lab policies and automated policy enforcement technology of client-adopted policies through Avalon's Routine Test Management (RTM) program. Of note, Avalon has demonstrated 10-20% annual savings in outpatient lab spend.

Health Plans Benefit from Avalon's End to End Routine Test Management Program

Avalon's Routine Test Management program streamlines the process of determining lab provider compliance with health plan lab policy, which in turn eliminates waste among high-volume, low-cost laboratory tests while ensuring that physicians and patients are unaffected.

- Grounded in science: Avalon's Lab Clinical Policies for outpatient lab tests are based on scientific research and undergo a rigorous review process.
- Clinical Advisory Board: Policies are updated annually or as science dictates by an independent Clinical Advisory Board (CAB) consisting of industry leaders in laboratory medicine.
- Policy approval and translation: health plan-approved policies are translated into codified rules and edits to ensure compliance with the health plan's standards. Avalon oversees the configuration of rules, ensuring they align with the health plan's approved policies and comply with quality and compliance standards.
- Program integrity through publication of the health plan's adopted policies and application of fixed, population-based criteria by way of industry standard claim edits that eliminate waste and drive compliance. During mid-adjudication, Avalon can identify with specificity when a lab provider's claim for reimbursement includes elements that violate the plan's adopted policies. All of this occurs within milliseconds.
- Provider education: Avalon provides education and tools to help providers adhere to policy, bill appropriately, and reduce burden.

Genetic Testing - Landscape Spend and Utilization

Genetic Testing - Spend Landscape

In 2023, the overall spend on genetic lab tests was $13.42 per member per year (PMPY). This analysis was based on a spend of $203 million from ~15 million members from Avalon clients across all books of business.

- This spend figure represents an 8% increase from $12.47 PMPY in 2022. This increased spend is mostly related to increased costs of genetic tests as well as an increased number of members receiving genetic tests rather than an increase in overall utilization.

Genetic Testing - Utilization Landscape

In 2023, the overall utilization of genetic lab tests was 2.84 tests per 100 members per year (PMPY).

- This analysis was based on utilization of over 428,234 tests among ~15 million members. This utilization represents a 5% increase from 2.70 tests per 100 members PMPY in 2023.

We analyzed Genetic Test Management for health plans engaged with Avalon in 2023 to look for patterns of utilization among members. In this subgroup analysis of 176,394 members who had at least one CPT code procedure for genetic testing over the year, we measured utilization and spend figures (Table 6).

Table 6. Genetic Tests Utilization and Spend Figures Among Members with at Least One Genetic Test in 2023

Category	Utilization PMPY	Spend PMPY
Mean	1	$975
Median	1	$562
Standard Deviation	2	$1690
Quartile 1	1	$102
Quartile 3	2	$998
Intra-quartile Range	1	$895

Reference. *Avalon data on file*

Key findings on spend:

- In 2023, the overall spend on genetic lab tests was $13.42 per member per year (PMPY). This analysis was based on a spend of $203 million among ~15 million members. This spend represents an 8% increase from $12.47 members PMPY in 2022.
- This increased spend is likely due to both the increasing costs of genetic tests as well as the increasing use of genetic testing. Given the fact that the growth in spend (8%) was greater than the growth in utilization (5%), it is likely that the increased cost of testing played a larger role here as well.
- Among members who had one or more genetic tests in 2023, the data demonstrate skewing towards high spend members, as the mean spend ($975) is greater than the median spend ($562) here. This finding is consistent with the wide range in costs among genetic tests.
- The large standard deviation and interquartile range observed also underscores the same high variability of spend patterns. This finding is likely due to the wide distribution of costs among genetic tests. This assumption on the importance of differing costs among genetic tests is confirmed by the findings of the utilization analysis, which showed that most members received only 1 test.
- In terms of outliers, the high outliers, representing a high spend value outside the overall pattern of distribution using the interquartile method, are members with spend greater than or equal to $2,340. In terms of outliers, the absolute highest outlier, representing the highest spend for any member in the 2023 analysis, was $56,635.

Key findings on utilization:

- In 2023, the overall utilization of genetic lab tests was 2.84 tests per 100 members per year (PMPY). This analysis was based on utilization of 203 million tests among approximately 15.1 million members. This utilization represents a 5% increase from 2.70 tests per 100 members per year in 2022.
- Among members who had one or more genetic tests in 2023, the mean number of tests per member (1) was the same as the median number of tests per member (1), a pattern of utilization without the skewing of test use towards high users seen in routine testing.
- The large standard deviation also points to a wide distribution of testing numbers per member. The large interquartile range also

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underscores the high variation of testing numbers in this population.

- In terms of outliers, the high outliers, representing high utilization outside the overall pattern of distribution using the interquartile method, are members with utilization greater than or equal to 3.5 tests in 2023. In terms of outliers, the absolute highest outlier, representing the highest utilization for any member in the 2023 analysis, was 58 tests.
- The mean number of encounters over the year was 1, suggesting that there was 1 genetic test ordered per office visit. This number contrasts with the 4-5 routine tests ordered per office visits.

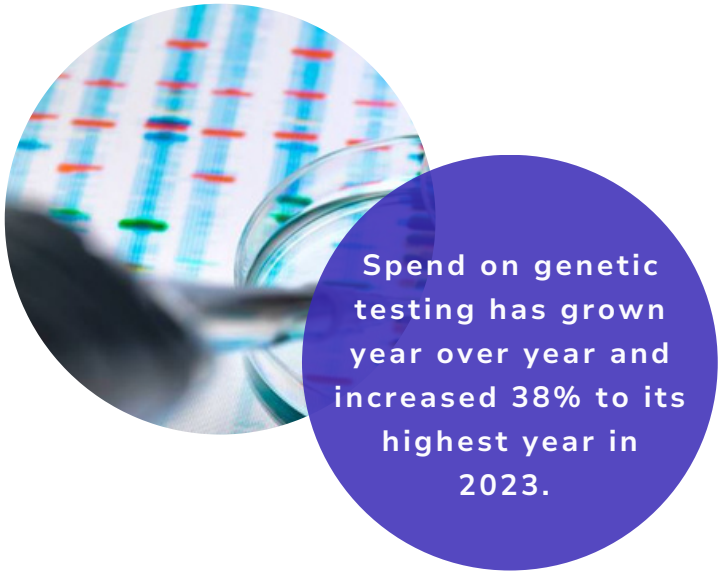
Genetic Testing - Spend and Utilization Trends

Genetic Testing - Trend in Spend

We analyzed spend and utilization for genetic tests among Avalon clients across all books of business for this analysis.

In 2023, the overall spend on lab tests was $13.42 per member per year (PMPY). This analysis was based on a spend of $203 million among ~15 million members.

- This spend represents an 8% increase from $12.47 PMPY in 2022 (see Figure 3 below).



- Overall spend was $9.75 per member per year in 2020 during the COVID-19 pandemic (decreased by 8% from 2019).
- However, since 2020, spend on genetic testing has grown year over year and increased 38% to its highest year in 2023.
- We believe that this increase in overall spend over time is mostly associated with an increase in the costs associated with genetic testing, as newer innovative tests are associated with increased costs as well as increased intended use populations.

We note from the literature on the trend in spend on genetic testing suggests that spend is expected to increase ~11% (range of estimates include 8-22%) per year for the next 5-8 years.[27]

Genetic Testing – Trend in Utilization

In 2023, the overall utilization of genetic lab tests was 2.84 tests per 100 members per year (PMPY). This analysis was based on utilization of over 428,234 tests among ~15 million members.

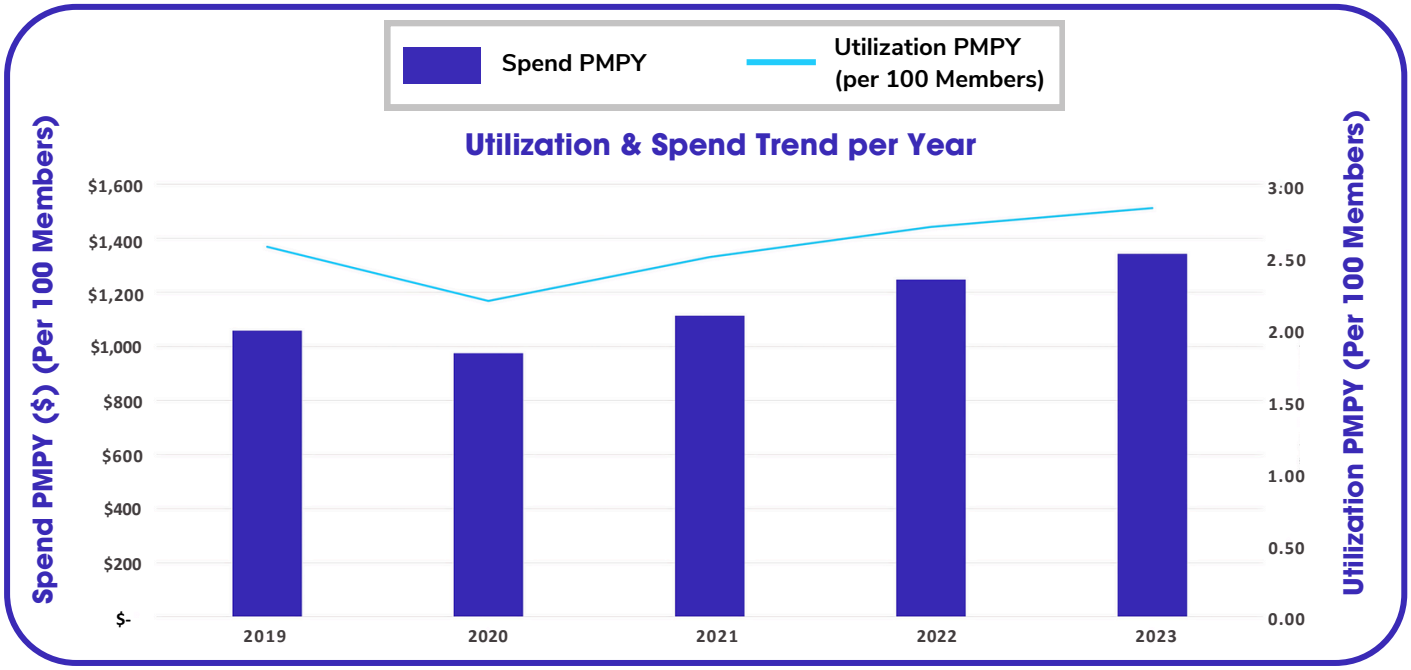
- This utilization represents a 5% increase from 2.70 tests per 100 members PMPY in 2022.
- Overall utilization was 2.19 per 100 members per year in 2020 during the COVID-19 pandemic (decreased by 15% from 2019).
- However, since 2020, utilization in genetic testing has grown year over year and increased 29% to its peak year in 2023.
- We believe that this overall increase in overall spend over time is associated with an:

  -Increase in the number of members receiving genetic testing.

  -Increase in attention by patients and providers in genetic testing overall.

  -Increase in the number of diseases such as cancer as well as a number of anti-cancer medications that are managed in a more optimized way using DNA and RNA blood tests.

Figure 3. Trends in Genetic Testing 2019 - 2023 Show an Increase in Spend and Utilization Noted Over Time



Reference. Avalon data on file

Legend. Both spend and utilization in genetic testing increased in 2023 versus 2022. Of note, peak changes in trend for utilization and spend occurred from 2020 to 2021, most likely due to depressed baseline numbers in 2020 due to pandemic-related events.

Key findings on trends in spend and utilization in genetic testing:

- In 2023, the overall spend on lab tests was $13.42 per member per year. This analysis was based on a spend of $203 million among ~approximately 15 million members. This spend represents an 8% increase from $12.47 PMPY in 2022.
- In 2023, the overall utilization of genetic lab tests was 2.84 tests per 100 members per year (PMPY). This analysis was based on utilization of over 484,000 tests among approximately 1.56 million members. This utilization represents a 5% increase from 2.70 tests per 100 members per year in 2022.
- Over the years 2019-2023, spend on genetic tests peaked in 2023, and utilization of genetic tests peaked in 2023. Spend and utilization were lowest in 2020.
- The percent increase in spend (38%) was greater than the percent increase in utilization (29%) over the 2019-2023 period.

Genetic Testing - Top 5 Compliant and Non-Compliant Codes

Molecular diagnostic testing and laboratory developed testing are rapidly evolving areas that present billing and coding challenges. Due to the rapid changes in this field, with as many as 10 new tests being developed and marketed each day in the U.S., the CMS Clinical Laboratory Fee Schedule pricing methodology does not account for the unique characteristics of these tests. Due to these challenges, services are being incorrectly coded and improperly billed.

Avalon recognizes this scenario and utilizes its laboratory policy team and independent Clinical Advisory Board to develop laboratory policies to meet the needs of the health plan. As part of its Precision Genetic Test Management program, Avalon leverages emerging industry standards to

identify discrete test quality and ensure consistent coding as well as automated policy enforcement through NCQA-certified prior authorization programs. This system better describes the ordered test and provides rules to optimize the usefulness and generalizability of the test and test results. The tables below address the top 5 compliant prior authorization codes as well as the top 5 non-compliant codes (Tables 7 and Tables 8, respectively).

The top five tests determined to be compliant by prior authorization represent the incarnate list of genetic tests used for prenatal and early infant care. Prenatal genetic carrier screening is reimbursable for the analysis for the presence or absence of the mutation associated with spinal muscular atrophy (SMN1, CPT code 81329); in addition, all newborns in the United States are now screened for cystic fibrosis (CPT code 81220). New to the list in 2023 of the top five compliant codes is CPT code 81443, which is associated with testing of 15 or more genes associated with severe inherited diseases.

Table 7. Top 5 Codes Determined to Be Compliant by Prior Authorization

Procedure Description (CPT Code)	Percent of Total Units Determined Compliant
SMN1 GENE DOS/DELETION ALYS (81329)	10.73%
CFTR gene com variants (81220)	9.87%
Hrdtry brst ca-rlatd dsordrs (81433)	6.67%
Hrdtry brst ca-rlatd dsordrs (81432)	6.53%
GENETIC TSTG SEVERE INH COND (81443)	4.12%

Reference. Avalon data on file

The top five tests determined to be noncompliant represent a combination of discriminate, non-well-defined codes often used with genetic test orders and approved codes, as shown above. For example, the CPT code 81479, the number one code in terms of noncompliant units at ~11% of units submitted for payment, represents an assortment of laboratory-derived tests without further description. Without more specificity, it is difficult to document and manage these tests.

Accordingly, there is a major opportunity for intervention by Avalon to help health plans understand what they are paying in addressing the CPT procedure code 81479, a code that is rising in frequency of use due to increased number of new genetic tests in the marketplace as well as uptake of recently marketed tests. Lab test manufacturers are required to use a procedure code that most accurately describes the service being rendered. If the genetic tests are not represented by a procedure code, the unlisted molecular pathology procedure code 81479 is used.

Lastly, there are several codes listed as noncompliant which seem to be clinically relevant as well as appear in the top five codes determined to be compliant by prior authorization. This scenario is accounted for by the work of Avalon to evaluate approved as well as unapproved codes in the Genetic Test Management program to minimize fraud, waste, and abuse.

Table 8. Top 5 Codes Determined to Be Noncompliant by Prior Authorization

Procedure Description (CPT Code)	Percent of Total Units Determined Non-Compliant
Unlisted molecular pathology (81479)	11.81%
Hrdtry brst ca-rlatd dsordrs (81433)	7.67%
Hrdtry brst ca-rlatd dsordrs (81432)	7.48%
BRCA1&2 GEN FULL SEQ DUP/DEL (81162)	2.67%
GENETIC TSTG SEVERE INH COND (81443)	2.47%

Reference. Avalon data on file

The top 5 tests determined to be noncompliant represent a combination of discriminate, non-well-defined codes often used with genetic test orders.

Avalon Can Help Manage Genetic Test Spend and Utilization

Avalon can assist health plans in addressing these outliers in terms of spend and utilization as health plans consider what genetic tests could be offered. Avalon offers health plans robust evidence-based lab policies and appropriate enforcement of adopted policies through its Genetic Test Management tools, NCQA-accredited, preservice review services, and network management.

The variable pricing of genetic testing is noted here, which may be addressed through preferred networks that allow for better cost monitoring.

Avalon has introduced the AvalonSelect Genetic Network to help health plans simplify Genetic Test Management and decrease costs and administrative burden while improving the quality of genetic tests provided to members.

- Avalon's genetic network is a select group of preferred genetic labs coupled with robust consultative services that complement a health plan's existing routine lab network.
- Health plans can continue to leverage their current lab relationships while outsourcing the management of genetic testing, pricing, compliance enforcement, test quality assessment, new lab technology evaluation, and contracting to Avalon.
- Savings of ~10+% on overall Avalon managed genetic test spend with a contracted preferred network and negotiated fee schedule may be achievable.

Genetic testing presents spend and utilization management themes, as suggested above, that differ from those used in Routine Test Management. Avalon has a broad Genetic Test Management program targeted to address these spend and utilization themes.

Health Plans Benefit from Avalon's Comprehensive Genetic Test Management Program

Avalon's Genetic Test Management program provides health plans with a comprehensive solution to manage the growth and costs of genetic testing while providing access and quality of care in this emerging field at a reasonable cost.

- Policy development: Avalon's proprietary, evidence-based policies for genetic labs validated by an independent Clinical Advisory Board
- Test identification and quality: a scalable framework to classify and evaluate genetic tests to ensure the right test is provided
- Utilization management: NCQA accredited preservice review as well as automated provider decisioning and clinical reviews based on health plan policies
- Program integrity/payment accuracy: automated claim coding rules to enforce plan adopted laboratory policies and validate authorization decisions during claim adjudication
- Genetic network management: a select group of preferred genetic labs coupled with robust consultative services that complement a health plan's existing routine lab network with vetted providers and pre-negotiated national fee schedule (as noted above with AvalonSelect Genetic Network).

Value to health plans:

- Minimize abrasion of plans, providers, and members by automating, or for select procedures, removing the requirement for prior authorization using gold-carding
- Reduce fraud, waste, and abuse
- Increase savings and reduce administrative burden
- Improve care quality by providing the correct test
- Steer members to higher-quality lab providers

Place of Service Matters

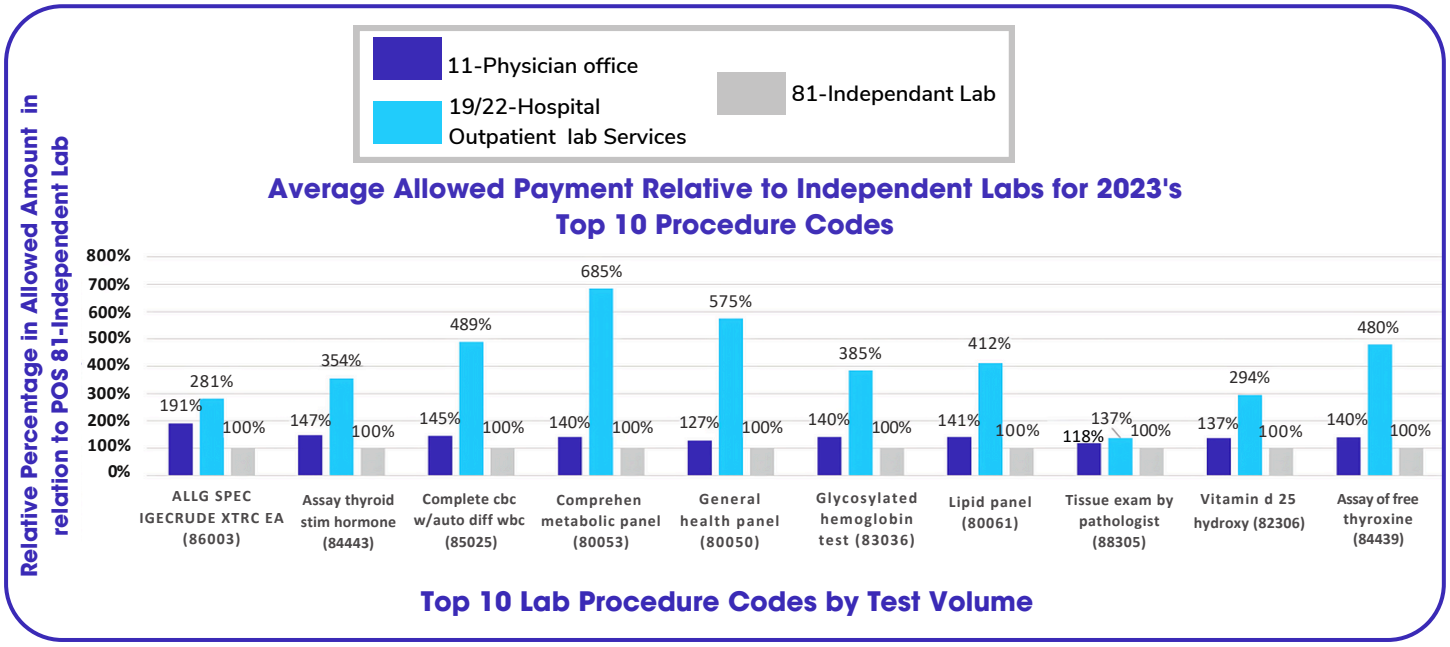
Place of Service (POS) Codes are two-digit codes placed on healthcare professional claims to indicate the setting in which a service was provided. The Centers for Medicare & Medicaid Services (CMS) maintain POS codes used throughout health care. This code set is required for use in the implementation guide adopted as the national standard for electronic transmission of professional health care claims under the provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).[28]

A study of employer-sponsored insurance found that prices for seven common services, such as office visits, chest x-rays, and MRIs, were 21-258% higher when delivered in a hospital outpatient department (HOPD) instead of a physician office.[29] The study also found that these price differences have been increasing over time. Similarly, lab test prices can vary dramatically depending on where it is performed. Both public and private insurance tend to pay a higher rate for lab tests when performed at a hospital outpatient lab department rather than an independent lab. Indeed, employer-based insurance typically pays three times more for clinical lab tests when billed by hospital outpatient departments compared to identical tests billed by physician offices and independent laboratories.[30] We examined these spend and trend themes in the Avalon database as outlined below.

For the top 10 routine tests by paid amounts, the physician office and outpatient hospital-based lab services were higher than the independent lab setting (Figure 4). The biggest differences were noted for the Complete Metabolic Panel measurement (CPT 80053) and Complete Automated Blood Count (85025) with automated differential measurement, which were among the top routine tests in terms of utilization. Importantly, there is no evidence that the increased costs associated with these routine tests in the outpatient hospital setting versus the independent lab setting provide added quality here. Rather, this lab testing is more akin to commodities and represents narrowly defined clinical care that is unaffected by the health status of patients or the ability of a hospital to distinguish itself on the quality of such services.[31]

Increases in the already inflated hospital outpatient lab services setting rose from 9 to 46% from 2022 to 2023.

Figure 4. Percent Difference in Average Allowed Payment for Independent Labs for 2023's Top 10 Procedure Codes



Reference. Avalon data on file

Description. When comparing lab charges for common routine tests, the hospital outpatient lab services site and physician office settings were more expensive than the reference (set at 100%) independent labs

This combination of scenarios, high differential price per setting and high utilization of testing along with no evidence of improvement in quality of care, compounds the costs for health plans and their members. Of note, not only is there a marked price price differential by site, but the magnitude of this price differential is also increasing over time. As noted in Table 9, increases in the already inflated hospital outpatient lab services setting rose from 9-46% from 2022 to 2023.

Table 9. Trend in Price Differentials Between Independent Lab and Hospital Outpatient Services

Service	Price differential of testing in hospital outpatient services (19/22) versus independent lab (81)		
	2022	2023	Increases 2023 vs. 2022
Basic & Comprehensive Metabolic Panel (80053)	626%	685%	9%
Complete Automated Blood Count (CBC) (85025)	423%	489%	16%
General Health Panel (80050)	395%	575%	46%
Lipid Panel (80061)	356%	412%	16%

***Reference.** Avalon data on file*

How Will Public Policy Impact the Price Differential of Lab Testing?

Because of the enormous cost differences associated with the same services offered in different facilities, a new policy proposal called site neutrality is increasingly popular on Capitol Hill.[32] One policy proposal passed by the U.S. House of Representatives in 2023 would make payments for health care services equal across all outpatient care settings, whether that be in a hospital-owned outpatient setting, a physician's office, or another outpatient setting.[33] In addition to the cost differential, some policymakers and experts believe that hospitals are being incentivized to acquire independently owned testing sites so they may be reimbursed a higher amount for identical lab testing services.[34] To date, no site neutral policies have been enacted into law and imposed across the federal landscape that addresses lab testing price differentials.

How Can Avalon Help?

Avalon contracts with independent laboratories, creating a broad network that supports client health plans. Excess laboratory spend can be avoided through point-of service optimization. Programs that drive utilization to independent labs can achieve marked cost savings in an administrative manner which is a natural combination with other measures to improve utilization overall.

Most patients and physicians are not aware of this and their potential savings. Avalon can provide education on pricing to drive more cost-effective care around lab testing.

CASE STUDY AND EXEMPLARS: AVERTED COSTS AND LAB VALUE MANAGEMENT

Lab Benefit Management Case Study - Averted Costs

The following is a case study examining actual averted costs associated with the Avalon rules engine and utilization management strategies for routine and genetic testing.

We analyzed Routine Test Management (RTM) for two health plans engaged with Avalon and its utilization management strategies in 2023. Of note, these two plans included ~4.5 million members. Spend on routine lab tests among these two health plans was $309,725,577 and averted costs were $32,026,351, representing a 10.3% relative cost savings and translating to an absolute savings of $7.08 PMPY or $0.59 PMPM (Table 10).

In a similar fashion, we analyzed Genetic Test Management (GTM) for these four health plans which were enrolled in Avalon's Genetic Test Management program and evaluated lab spend in 2023 among these health plans. Of note, these four plans included ~6.1 million members. Spend on genetic lab tests among these four health plans was $110,471,107 and averted costs were $38,732,897, representing a 35.1% relative cost savings and translating to an absolute savings of $6.34 PMPY or $0.53 PMPM (Table 10).

Table 10. Total Lab Spend and Averted Costs Using Avalon's Routine Test Management (RTM) and Genetic Test Management (GTM) Programs Showed Savings

Product	Total Spend	Averted Costs	PMPY Savings	Overall Savings
GTM	$110,471,107	$38,732,897	$6.34	35.1%
RTM	$309,725,577	$32,026,351	$7.08	10.3%

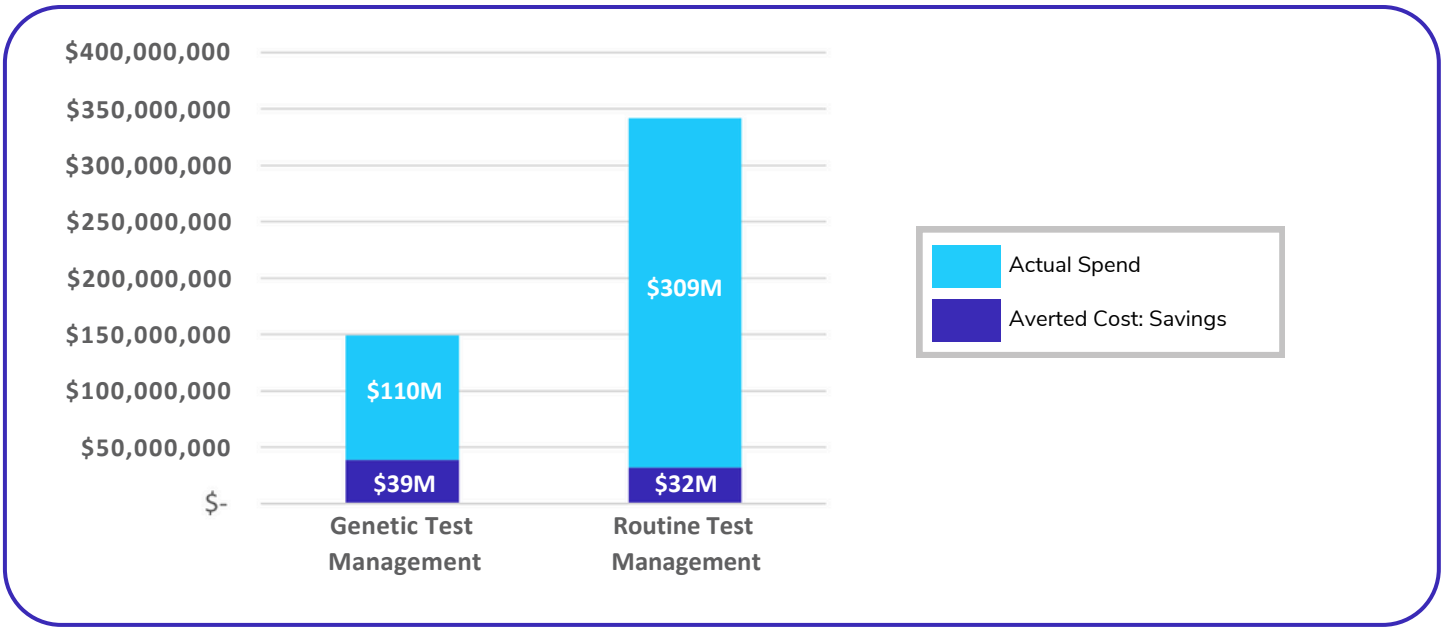
Reference. *Avalon data on file*

The averted costs for the RTM program were only slightly higher than that of the GTM program, despite total spend was more than 3x higher for routine tests versus genetic tests (Figure 5). This finding illustrates the fact that although genetic testing makes up 30% of overall lab testing, high price genetic tests can be efficiently managed by Avalon and result in substantial savings.

Additionally, in this illustration, averted costs were approximately 17% ($70,759,248 averted costs/ $420,196,684 total spend) of total lab spend.

In addition to averted costs as described above, Avalon's GTM and RTM solutions drive 5% - 15% lab behavior change, which further increase health plan savings.

Figure 5. Comparison of Averted Costs for RTM and GTM Selected Member Population



Reference. *Avalon data on file*

Legend. *Sum of averted costs for the GTM program were approximately the same as averted costs from the RTM program; however, given the small denominator (less spend) on genetic tests, the averted costs savings on a relative percentage basis were significantly higher for the GTM over the RTM program.*

Lab Values Management – Leveraging Lab Value Insights to Impact CKD Early Detection, Care Outcomes, And Costs

Introduction

Chronic Kidney Disease (CKD) is one of the most common illnesses (more than 1 in 7 U.S. adults have CKD). It may be surprising, but 90% of patients are not aware of their CKD diagnosis. Another 40% of people with severely reduced kidney function are not on dialysis. CKD is a significant cost driver, with annual Medicare costs of $124.5 billion.[35]

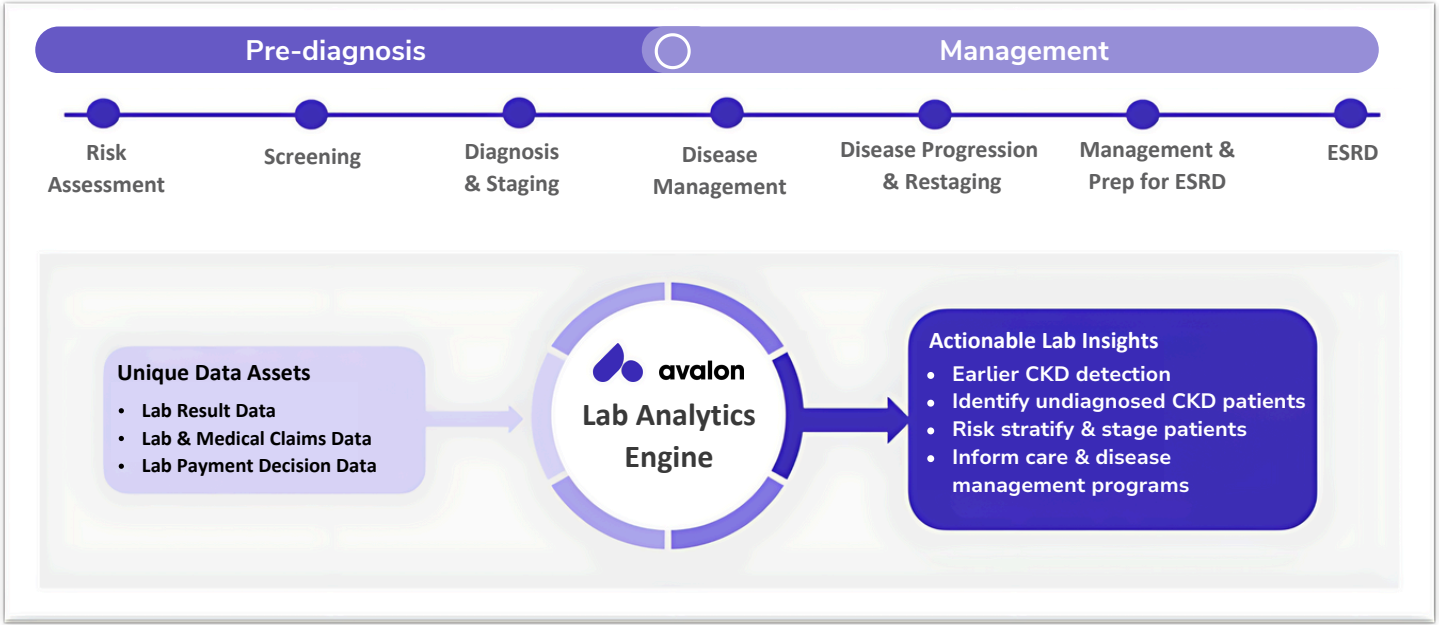
Lab value data and derived insights can have a meaningful impact on CKD member costs and outcomes.

Opportunities

Despite the cost of diagnosing and treating CKD patients, most health plans and CKD care management programs are not focused on the most cost-effective solutions for delaying disease progression. Combining lab values with the appropriate action steps in patient care provides the ingredients for CKD lab value insights.

- Identify high-risk, undiagnosed and non-staged members across all CKD stages earlier in the process using lab values
- Leverage actionable insights to enhance the impact of care management to inform health plan programs.

Figure 6. The Interaction Between Avalon Program in CKD and the CKD Patient Journey Is Active Throughout



Reference. *Avalon Healthcare Solutions*
Description. *From risk assessment to end-stage renal disease (ESRD), data contributes to the Lab Analytic Engine to provide actionable lab insights*

Avalon's Lab Values Management approach here addresses three key drivers to improve outcomes while reducing costs.

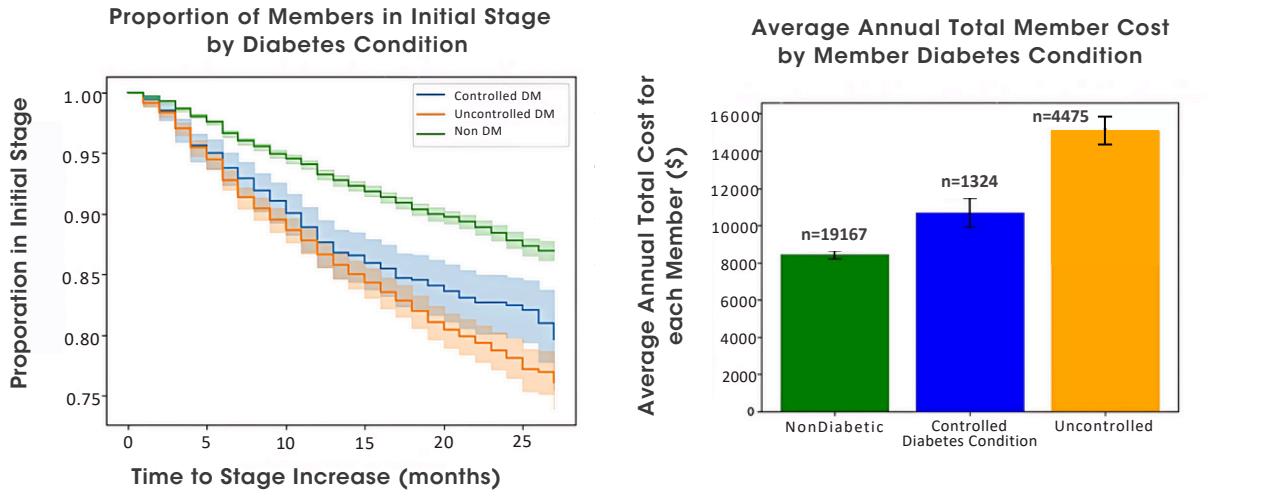
Driver 1 - Underdiagnosis and Understaging

In an Avalon case study from a commercial health plan, a member analysis found that 11,000 were undiagnosed or unstaged. Those members can now be followed by their providers for diagnosis and, if indicated, prevention of kidney disease progression and improved management of diabetes and hypertension. Within the program's first year, projected savings are $979 per Stage 4 member.

Driver 2: Uncontrolled Diabetes and Hypertension

Most CKD care management programs do not focus on the key factors at a patient level that contribute to disease progression: uncontrolled diabetes and hypertension. Control of these factors known to speed the progression of CKD can lead to quality and cost benefits.

Figure 7. The Effect of Uncontrolled Diabetes in CKD Patients

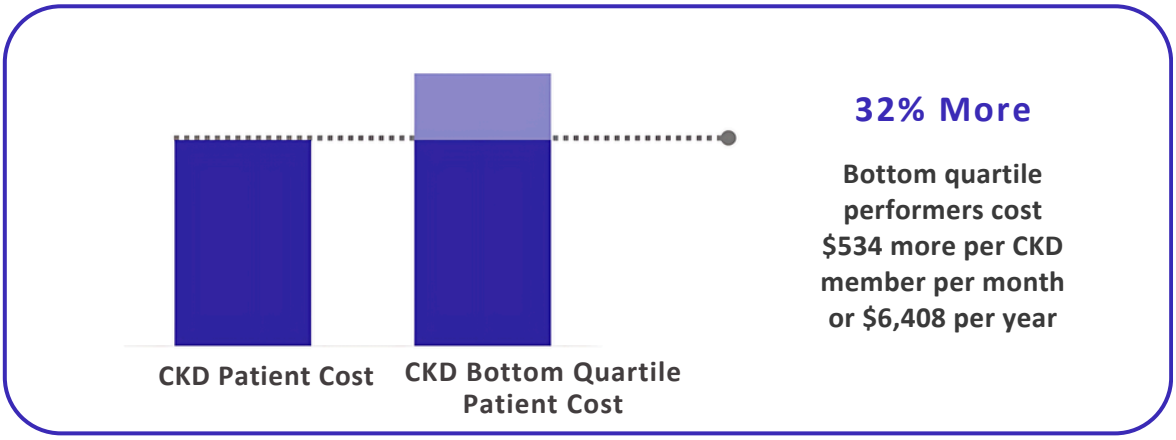


Reference. *Avalon data on file*
Legend. *Patients with uncontrolled diabetes progressed faster to the next stage of CKD and had costs that were ~50% higher as compared to patients with controlled diabetes.*

Driver 3: Misaligned Nephrologist Incentives

Many failed value-based care programs have focused on wrap around services that are out of the control of nephrologists. Avalon's physician-designed and led approach benchmarks physician performance, allowing for the evaluation of physician performance incentives and shared savings. Analysis of Avalon's nephrologist quality benchmarks shows that the bottom quartile performers cost $534 (32%) more per CKD member per month.

Figure 8. The Opportunity Is Present to Improve Quality and Cost



Reference. *Avalon data on file*
Description. *There is a strong association between less-than-optimal quality and increased care costs.*

What Are the Benefits of this Program?

CKD is a multi-faceted problem requiring a multi-disciplinary and data-driven approach. This scenario underscores the importance of early intervention, provider engagement, and a commitment to value-based care for improving patient outcomes and reducing costs. Avalon Healthcare Solution's access to lab claims data and lab results data, coupled with our extensive lab expertise, provides a unique ability to derive critical insights for the early detection and intervention of CKD.

Avalon applies its proprietary analytic model and algorithms to lab result values and claims data to identify and stratify high-risk CKD patients for health plans and providers. Avalon's lab insights inform the patient care journey and complement existing care and disease management programs with increased and earlier identification of CKD patients.

In summary, the benefits of the Lab Value Management program include:

- Early identification of patients by identifying members in stage 3 and beyond who had not previously been identified. Laboratory values provide the opportunity for early detection, as lab claims per se do not provide enough information for this type of detection.
- Value-based alignment through early patient identification and intervention that aids providers under existing value-based reimbursement models to better care for their patients.
- Data-driven decisions brought about by data leading to more actionable insights. This actionable data allowed for changes in clinical decision-making.
- Complex management through attention to quality improvement in diabetes and hypertension care, which are leading causes of CKD. This data can facilitate the roles of primary care and nephrology in a multi-disciplinary approach.
- Trust and science by leveraging data to build relationships with the provider community. The data also provides feedback needed to facilitate discussions for care management within a health system.
- Movement towards the Triple Aim of clinical care using lab value data for earlier detection and CKD staging. The result can be improved quality, increased access, and decreased costs of care for CKD patients.

CKD is a multi-faceted problem requiring a multi-disciplinary and data-driven approach.

Lab Values Management – Improving Quality and Total Cost of Care in Oncology

Introduction

Cancer is one of the deadliest - and most expensive - diseases on our planet. Fortunately, early and accurate lab diagnostic methods can lead to better clinical care outcomes. For example, mutation analyses in cancers with targeted therapies are significantly underutilized. As a result, chemotherapy selection, overall costs, and outcomes may be adversely affected. Administrative challenges around ordering mutation testing on tissue samples may be contributing to this problem.

The goal of leveraging lab values and derived insights in oncology is to help providers, health plans, and patients use genomic test results and lab-informed cancer treatment from start to finish to improve outcomes.

Opportunities

Several opportunities exist to improve cancer care through the patient journey from biopsy to lab to diagnosis to results to specialty medications options to drug administration. An informed use of an approved set of genetic tests based on diagnosis, as well as the approved set of drugs based on diagnosis and genetic test results, can help improve outcomes across the care continuum.

Several challenges exist in this model, including:

- Costs to reach optimal treatment regimen
- Drug mismatch based on lab values
- Inappropriate use of marker drugs
- Underutilization of genetic testing
- Underutilization of liquid biopsies

Several potential interventional opportunities exist in this model, including:

- Timely and accurate treatment provides health and financial benefits
- Better matching leads to better quality outcomes and decreased waste in drug spend
- Incorporation of genetic testing helps ensure the right drug for the right patient
- Savings opportunities can be achieved via a targeted increase in genetic testing
- Identifying mutations more effectively leads to savings opportunities

With respect to the costs of optimal treatment, timely and accurate treatment can provide health benefits as well as financial benefits. More specifically, delays in getting to the optimal treatment led to cancer progression, harmful side effects, and wasted spend on ineffective chemotherapy drugs.

- A JCO study of non-small cell lung cancer (NSCLC) members demonstrates next-generation sequencing (NGS) testing has an average up-front additional cost of $1,200, but members with broader panels saw savings of $8,500 PMPM.[36]
- Another study of NSCLC members shows that NGS testing versus sequential testing resulted in savings in TCOC of >$100K per commercial member.[37]

With respect to underutilization of genetic testing, there was a savings opportunity that can be realized via a targeted increase in genetic testing. More specifically, an undertested population could be on an inappropriate drug that does not match tumor mutation.

- A 30% improvement in properly testing high-risk breast cancer members could save $165 PMPM.[38],[39]
- A retrospective study showed that as few as 18% of NSCLC patients received all NCCN (National Comprehensive Cancer Network) recommended gene mutation tests.[40]

What Are the Benefits of this Program?

A lab values management program in oncology could lead to improved logic between tumor mutation and drug matching, faster time to the right treatment for the right patient, and treatment at a reasonable cost. Health plans that work with Avalon can develop prescriptive approaches to liquid biopsies, selective elimination of prior authorizations, negotiated rates for genetic testing, and auditing and analytics.

EMERGING THEMES

The 2024 Avalon Lab Trend Report demonstrates how clinical laboratory testing is changing in the face of technological advancements, shifting healthcare needs, and focusing on precision medicine. The following section explores a few emerging issues that affect both the clinical laboratory as well as all of those who depend on the clinical laboratory for the health of their patients. These emerging issues include two issues we addressed in the 2023 Lab Trend Report: multicancer early detection (MCED) tests and polygenic risk scores (PRS). We also review advances in blood biomarker testing and the FDA's plan to regulate lab-developed tests (LDTs).

Multicancer Early Detection (MCED) Tests

In the Lab Trend Report 2023, we introduced the theme of future lab tests under development in genetic testing. Both multicancer early detection (MCED) tests and polygenic risk scores (PRS) address preventative strategies and are considered screening tests using DNA analysis to provide information on the risk of disease in patients without

any current signs or symptoms suggesting a cancer diagnosis MCED tests are not new: a blood test for cancer screening has been the 'holy grail' ever since the carcinoembryonic antigen blood test in the 1960s was claimed to have nearly 100% sensitivity and specificity — but turned out not to — for colorectal cancer.[41]

What Is a MCED Test?

MCED (multi-cancer early detection) tests are a type of liquid biopsy that uses a sample of blood to identify specific biologic signals released by cancer cells in the blood.[42] MCED tests differ from other cancer screening tests in two main ways. First, they use a single blood test instead of X-rays, imaging tests (such as mammography), or other medical procedures (such as colonoscopy). Second, they check for many types of cancer from different organ sites at the same time - including some cancers that existing screening tests do not check for. Current MCED tests in development measure different biological signals in blood plasma, such as[43]:

- Changes in DNA and/or RNA sequences
- Patterns of DNA methylation (a chemical change to DNA which changes how the gene product is expressed)
- Patterns of DNA fragmentation (how the DNA is broken into smaller pieces)
- Levels of protein biomarkers
- Antibodies that a person's body may develop against components of growing cancer cells

In a systematic review of the predictive ability for cancer of cell-free-nucleic acid-based MCED tests, the authors noted that relatively few published studies have assessed the analytical and clinical validity of MCED tests.

What Are the Risks and Harms of MCED Tests?

Before clinical utility can be established, the ability of an MCED test to predict cancer status must be demonstrated. In a systematic review of the predictive ability for cancer of cell-free-nucleic acid-based MCED tests,[44] the authors noted that relatively few published studies have assessed the analytical and clinical validity of MCED tests. For almost all studies identified in this review, the cancer cases were assessed at time of diagnosis. It is important that test performance from clinical trials be derived from individuals who represent the intended use population. In addition, most data indicate that MCED tests are better at detecting later-stage cancer than early-stage disease. A deep understanding of the benefits and risks of MCED-based screening requires a randomized controlled trial.[45]

Potential benefits include:

- Ability for cancer screening at organ sites currently without an available screening test
- Earlier detection of cancer with potential to improve patient outcomes
- More convenient screening for multiple cancers at the same time through a single blood draw
- Less invasive procedures for cancer screening

Potential risks include:

- False-negative results leading to a delay in treatment
- An MCED test may report a negative result when the person has a cancer. This could lead to a delay in cancer treatment if the MCED results provide a false sense of confidence that leads a person to ignore symptoms.
- False-positive results leading to further unnecessary testing
- Overdiagnosis and overtreatment of slow growing tumors

What Are the Current Updates in this Emerging Area?

While MCED tests are very new, public policy is

driving support for its widespread clinical use. In 2023, the Federal Trade Commission (FTC) issued an Order[46] requiring Illumina to divest its interest in GRAIL, which makes a multi-cancer early detection (MCED) test. The FTC found, and a federal appeals court agreed, that Illumina's acquisition of Grail would diminish innovation in the U.S. market for MCED tests while increasing prices and decreasing choice and quality of tests. In December 2023, Illumina announced its decision to divest its interest in GRAIL.[47]

In addition, there are no professional medical societies or guidelines that have issued recommendations on the use of MCED tests for cancer screening. At least three MCED tests have received a Breakthrough Device Designation from the FDA, and an FDA decision on one of these products is expected in the first half of 2024.

A key feature of such a trial is determining the clinical utility of MCED tests by measuring whether the tests result in fewer cancer deaths in the population of screened individuals compared to a control population. A large study population is needed to address this theme. Several trials to investigate this theme are underway:

- In June 2022, the NCI Board of Scientific Advisors approved a proposal to create a Cancer Screening Research Network (CSRN), a new network of organizations that includes healthcare systems, military healthcare, and academic institutions, federally qualified health centers, and at least one tribal nation. The CSRN will conduct rigorous, multi-center cancer screening trials and studies with large and diverse populations in a variety of healthcare settings with the ultimate goal of reducing the number of cancer-related deaths and illnesses.
- In 2024, the Cancer Screening Research Network (CSRN) will begin enrolling up to 24,000 healthy people aged 45-70 in a Vanguard study to assess the feasibility and finalize the design and logistics for a later, larger study.
- The National Cancer Institute is also studying the benefits of MCED tests and will sponsor a large trial in 2024 scheduled to enroll 24,000 healthy people in a pilot study. If MCED tests are found to be useful, a larger study of up to 225,000 people will be set up.

How Can Avalon and Payers Work Together on Innovations in Lab Tests?

As mentioned above, there are at least three MCED tests that have received a Breakthrough Device Designation from the FDA and an FDA decision on one of these products is expected in the first half of 2024. Factors favoring the implementation of MCED testing using a simple blood draw include:

- MCED tests used for screening can replace higher cost and/or more invasive screening methods of today.
- MCED tests provide the opportunity for early detection of cancer, and outcomes of cancer care are greatly improved when early diagnosis is available.
- As healthcare standards move towards personalized medicine, we anticipate that the MCED test as a cancer indicator will become more prevalent.

Conversely, health plans should also proactively address desired use criteria for their members, given the ease of use and potential overuse (i.e., avoidable waste) of simple blood tests to screen for cancer.

Avalon can help health plans with their determination of appropriate coverage for these tests for their members. In the policy development phase, Avalon conducts a deep dive into the clinical validity and clinical utility of new and evolving blood tests to help determine the usefulness and generalizability of these tests in a real-world setting.

- Clinical validity studies focus on answering the question, "Does the test measure what is intended to measure?" For MCED tests, the question is whether the test result identifies cancer as measured against gold standard

technologies such as tissue biopsy and standard of care screening tests.

- Clinical utility studies focus on answering the question, "Does the test result lead to a change in patient behavior of health care provider decision making, and/or does this change lead to better outcomes?" These studies are needed to establish the addition of the lab test to the usual care pathway for the patient and the healthcare provider in a way to justify the logistics and costs of their implementation and use.

Polygenic Risk Score (PRS) Tests

In the 2023 Lab Trend Report, we introduced the theme of future lab tests under development in the area of genetic testing. Both multicancer early detection (MCED) tests and polygenic risk scores (PRS) address preventative strategies and are considered screening tests using gene analysis to provide information on the risk of disease. Polygenic risk scores can provide a measure of disease risk across several chronic diseases: the premise is that patient and healthcare provider knowledge afforded by these precision medicine initiatives can help with management plans to identify individuals at high risk for disease and implement management plans to prevent disease.[48]

What Is a PRS Test?

A polygenic risk score (PRS), sometimes called polygenic score (PGS) or genetic risk score (GRS), represents a genome-wide measure of individuals' genetic propensities for diseases that, combined with other lifestyle factors, can give a better idea of how likely one is to get a specific condition. Significant technological and methodological advances since the Human Genome Project are facilitating population-based comprehensive genetic profiling at decreasing costs.

Polygenic risk scores are:

- Estimates of the genetic risk of an individual for some disease or trait, calculated by aggregating the effect of many common variants associated with the condition.
- Increasingly available given the genetic data now available in large cohort studies.[49]
- Described as single result reflecting the cumulative weighted risk of individual genetic variation for a set of traits. These individual genetic variants confer an incrementally small disease risk, but summated, they have been shown to be predictive of many chronic conditions.

For example, polygenic risk scores will be different for each specific disease. An individual may have a low or average genetic risk for one condition (e.g., 0.5-1 times the risk of a typical individual in the cohort), such as coronary artery disease, but at increased genetic risk (e.g., 2-3 times the risk of a typical individual in the cohort), for another condition, such as colorectal cancer.

In contrast, monogenic risk variants are typically a single, protein-truncating gene mutation conferring a relatively large risk of disease. Examples of monogenic risk variants for low density lipoprotein receptor (LDLR) gene mutation resulting in premature cardiovascular disease secondary to familial hypercholesterolemia or a F5 gene mutation resulting in deep vein thrombosis or pulmonary embolism secondary to Factor V Leiden.

Avalon can help health plans with their determination of appropriate coverage of new emerging tests for their members.

What Are the Risks and Harms of PRS Tests?

Polygenic risk scores can be a valuable tool for adding information to improve the care and management of patients with signs or symptoms of disease but may have increased likelihood to develop disease secondary to their genetic profile. Polygenic risk scores are now directly available to individuals to assess type 2 diabetes risk, measure elite athletic endurance, and determine the likelihood of depression, among other traits, without a healthcare clinician serving as an intermediary.[50]

There are concerns about the widespread use of PRS testing, either as direct-to-consumer testing currently available or as clinician-ordered testing in the near future, including:

1. Test accuracy

A secondary analysis of 3915 performance metric estimates for 926 polygenic risk scores for 310 diseases to generate estimates of performance in population screening, individual risk, and population risk stratification.[51] Polygenic risk scores performed poorly in population screening, individual risk prediction, and population risk stratification.

2. Lack of strict regulatory or quality oversights

While the FDA has the authority to regulate DTC products, one of the main reasons many PRS-based DTCs go unregulated is that they are marketed as general wellness products, which the FDA claims don't fall under its purview.

3. Unnecessary downstream testing

Concerns about consumers' misunderstanding of the tests' accuracy or utility, as well as clinician's appropriate actions to a false negative or false positive result from PRS testing, can lead to unnecessary, prolonged, and resource-intensive patient journeys as part of the resultant care pathway.

Clinician's actions to a false negative or false positive result from PRS testing, can lead to unnecessary, prolonged, and resource-intensive patient journeys.

What Are the Current Updates in this Emerging Area?

Coronary Artery Disease is perhaps the most studied cardiovascular phenotype for PRSs. Among middle-aged adults, a CAD PRS performs similarly to conventional risk factors and provides additional prognostic information for CAD. In a real-world implementation study of 832 individuals, the feasibility, acceptability, and impact of an integrated risk tool for cardiovascular disease (CVD IRT, combining the standard QRISK®2 risk algorithm with a polygenic risk score) was evaluated within routine primary practice in the UK National Health Service. Amongst HCPs and participants who agreed to the trial of genetic data for refinement of clinical risk prediction in primary care, the study authors observed that CVD IRT implementation was feasible and well accepted. The CVD IRT results were associated with planned changes in prevention strategies.[52]

A commercially available test is on the market today that claims to identify an individual's risk of developing 11 different types of hereditary cancers, including breast, uterine, prostate, or colorectal cancer. More than 200 different PRS are in development today, covering a wide variety of chronic diseases, including cancers, cardiovascular diseases, and neurological diseases. Some of these tests may be priced in the $1,000 range per the individual's genetic information and resultant PRS.

How Can Avalon and Payers Work Together on Innovations in Lab Tests?

While this technology and the data to support its use are still emerging, health plans would be wise to monitor this space. Factors favoring the implementation of PRS testing using a simple blood draw include:

- PRS tests used for screening have the potential for replacing higher cost and/or more invasive screening methods of today.
- PRS have shown their value in enabling greater differentiation into risk pools, thus providing the potential to right-size care to the right patient at

the right time.

- As healthcare standards move towards personalized medicine, we anticipate that PRS as a chronic disease predictor will become more prevalent.

Conversely, it will also be important for health plans to proactively address desired use criteria for their members, given the ease of use and potential overuse of simple blood tests to screen for cancer.

Avalon can help health plans determine appropriate coverage and reimbursement for these tests for their members. In the policy development phase, Avalon assesses the clinical validity and clinical utility of new and evolving blood tests to help determine the usefulness and generalizability of these tests in a real-world setting.

- Clinical validity studies focus on answering the question, "Does the test measure what is intended to measure?" For PRS tests, the question is whether the test result identifies patients at higher risk that are likely to develop the target condition in the represented time interval.
- Clinical utility studies focus on answering the question, "Does the test result lead to a change in patient behavior of health care provider decision making, and/or does this change lead to better outcomes?" These studies are needed to establish the addition of the lab test to the usual care pathway for the patient and the healthcare provider in a way to justify the logistics and costs of their implementation and use.

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Blood Biomarker Tests: the Future Is Here Today

The basic definition of a biomarker can be stated plainly as a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention."[53] Biomarkers are markers for a condition, disease, or aberrant process and can be discovered, for example, in tissues, body fluids, or blood. Clinical biomarkers, therefore, can have a significant role in narrowing or guiding downstream treatment decisions.[54]

The definition of a biomarker, as outlined above, is broad and could include routine tests and markers such as hemoglobin A1c and serum lipid levels. For this discussion, the focus will be on blood biomarker use in precision medicine, as such biomarkers have the potential to provide marked and impactful information based on the advances of the Human Genome Project, and more yet come to the market at a premium price.

Avalon can help health plans determine appropriate coverage and reimbursement for tests for their members. In the policy development phase, Avalon assesses the clinical validity and clinical utility of new and evolving blood tests to help determine the usefulness and generalizability of these tests in a real-world setting.

Why Is It Relevant?

Precision health is anchored in three pillars: personalized treatment plans, targeted therapies for improved outcomes, and minimizing side effects to elevate patient experiences. The importance of accurate biomarker testing in this concept is key, as such biomarkers in the development of precision medicine provide a strategic opportunity to improve human health and reduce healthcare costs. In addition, this three-pillar approach can get the right treatment to the right patient at the right cost through optimal laboratory medicine followed by optimal downstream clinical decision making. Overutilization and underutilization of healthcare resources are addressed in such a model, too.

To date, biomarkers in precision medicine are primarily used in prenatal testing, such as inherited traits and rare disease assessment, and oncology, including liquid biopsies and companion diagnostics. Recent developments outline a rapidly evolving

range of assays and systems to facilitate care, such as:

- Cardiac biomarkers – leptin gene for prognosis from coronary disease to heart failure
- Infectious disease biomarkers - sepsis diagnosis, bacterial v. nonbacterial etiology
- Central nervous system disease biomarkers – Alzheimer's disease, Parkinson's disease

Of particular interest is the introduction of blood tests that screen for Alzheimer's disease. In July 2023, the FDA granted approval for the drug Leqembi to treat patients with Alzheimer's Disease, which has spurred companies like C2N Diagnostics, LabCorp, and Quest Diagnostics to announce blood tests that screen for Alzheimer's biomarkers.

What Is the Opportunity to Improve Patient Care?

Biomarkers in precision medicine can be described in terms of their role in the clinical care process. A biomarker may be classified by its function in clinical decision making, such as[55]:

- Diagnostic biomarker – detects or confirms the presence of disease or condition
- Monitoring biomarker – provides for serial assessment of evidence of exposure or treatment effect
- Pharmacodynamic/response biomarker – measures the effect of exposure to a product or treatment
- Predictive biomarker – defines individuals who are more likely to receive favorable/unfavorable effects from exposure or drug treatment
- Prognostic biomarker – identifies the likelihood of a clinical event
- Safety biomarker – detects the presence or likelihood of an adverse effect
- Susceptibility/risk biomarker – indicates potential for developing disease

In 2015, the term digital biomarker was introduced: a digital biomarker provides information on normal and pathological biological processes using data collected from digital health technologies.[56] Because digital biomarker data can be easily collected outside of the routine healthcare setting, these biomarkers offer the opportunity to collect real-world objective, relevant data in a convenient and patient-friendly manner.

What Are the Challenges?

Given the all-encompassing nature of biomarkers as described above, there remains significant confusion regarding fundamental definitions and concepts involved in their use in clinical care. Furthermore, with new biomarkers developed and launched into the diagnostic and prognostic landscape daily, it is important to determine the optimal placement and implementation of these tests in the patient journey. Furthermore, 14 states have enacted biomarker laws requiring state-regulated health plans to cover comprehensive biomarker testing. While designed to increase biomarker test coverage for patients, the broad language used in several of these laws varies from state to state and ends up "legislating clinical utility" by enumerating what evidence insurers must consider in making coverage decisions.[57]

How Can Avalon Help with These Technologies?

Avalon can help health plans determine appropriate coverage and reimbursement for these tests for their members. In the policy development phase, Avalon conducts a deep dive into the clinical validity and clinical utility of new and evolving blood tests.

Clinical validity studies focus on answering the question, "Does the test measure what is intended to measure?" How do these tests stack up against gold-standard technologies? Clinical utility studies focus on answering the question, "Does the test result lead to a change in patient behavior of health care provider decision making, and/or does this change lead to better outcomes?" These studies are needed to establish the addition of the lab test to the usual care pathway for the patient and the healthcare provider in a way to justify the logistics and costs of their implementation and use.

Health plans would be wise to monitor this space as

these advanced biomarker tests are creating new indications for use (thus affecting utilization) as well as launching at a higher cost and/or more invasive screening methods of today (thus affecting price and mix). Conversely, it will also be important for health plans to proactively address desired use criteria for their members given the ease of use and potential overuse of blood biomarker testing for cancer, cardiac, neurology, and prenatal clinical care.

With the explosive growth of LDTs, there has been an ongoing debate about the best way to regulate them.

FDA Regulation of Lab Developed Tests (LDTS)

What Are Lab Developed Tests?

LDTs are diagnostic tests that are developed, validated, and performed in-house by individual laboratories. Some LDTs are routine tests, such as opioid testing for addiction medicine services, to more complex molecular and genetic tests for cancer, heart disease, and rare and infectious diseases. LDTs are critical in providing timely patient access to accurate and high-quality testing for many conditions for which no commercial tests exist, or where an existing FDA-approved commercial test does not meet current clinical needs. Overall, the thousands of LDTs performed at U.S. laboratories provide physicians with important clinical information to diagnose and treat patients, and these tests are essential to the practice of all areas of medicine.

What Is Significant About LDTs Right Now?

Decades ago, federal laws established parameters for patient safety for in vitro diagnostics (IVDs) and clinical laboratory operations, but they did not focus on tests created by individual laboratories. With the explosive growth of lab-developed tests (LDTs),[58] the Theranos case,[59] and the pandemic, there has been an ongoing debate about the best way to regulate LDTs.

On October 3, 2023, the FDA proposed a rule that would allow the agency to approve or reject LDTs as it does medical devices. The FDA argued that the rule is warranted, given the more diverse population that utilizes LDTs and an increasing reliance on high-tech instrumentation and software. Many lab stakeholders raised concerns over the FDA's Proposed Rule nearly immediately after it was published. In particular, a group of experts from Yale highlighted the potential unintended consequences of the proposed rule, including restricted access to rare-disease tests and delayed responses to future pandemics.[60] The experts—and other lab stakeholders—worry that regulating LDTs will place undue burden on Academic Medical Centers (AMCs), which were essential in developing COVID-19 tests early on in the pandemic. There is also skepticism that the FDA has the legal authority to issue the rule.[61]

On May 6, 2024, the FDA published a final rule to amend its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act), including when the manufacturer of the IVD is a laboratory. Effective on July 5, 2024, the rule would allow the FDA to begin phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs. It is expected that stakeholders will challenge the rule in court, but if the rule goes into effect, it will dramatically change the regulatory landscape for LDTs.

FROM THE DESK OF PAMELA STAHL

President, Avalon

Avalon's fourth Lab Trend Report continues our trend of defining and leading the Lab Benefit Management industry. Our mission is to leverage laboratory science, innovation, and technology to bring novel insights on the latest lab trends and to provide solutions to payers.

The takeaways from this report are:

- Lab testing is an essential part of the patient journey and will matter more going forward
- Routine testing accounts for 90% of lab testing utilization but spend per member was 3.6x higher on genetic testing ($273 versus $975)
- The location of lab testing makes a big difference in price
- Looking into the future – blood biomarkers are a bigger portal to assessing health and managing disease
- Avalon is the right partner to address lab testing utilization and quality issues

Every day, we work to help our clients reduce waste in routine testing and assist with the challenging arena of genetic test decision-making. Avalon is launching new services to assist payers with value-based care. By digitizing laboratory results and integrating them into our advanced analytics, Avalon can provide earlier disease detection to drive treatment protocols and reduce the per-member cost of healthcare.

Avalon knows that managing your lab benefit means much more than managing unit cost. If you would like to discuss your Lab Benefit Management strategy or see how Avalon's solutions can help your organization, please reach out to me: pamela.stahl@avalonhcs.com. ■

> **Every day, we work to help our clients reduce waste in routine testing and assist with the challenging arena of genetic test decision-making.**

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