Working Group on In Silico Reference Files

May 2023

ISRF

VIEWPOINTS

Exploring the use of in silico reference files in clinical trials

As the use of biomarkers is now increasingly standard of care in the diagnosis and treatment of cancer, clinical and well-characterized wet laboratory reference samples are important in helping laboratories and test developers ensure their assays detect and report the right biomarkers to inform treatment decisions. In silico reference files (ISRFs)–and specifically the manipulated assay data-based ISRF methods described in the Association for Molecular Pathology (AMP) and partners' 2022 recommendations[1]–can serve as a supplemental means for laboratories and test developers to validate and assess the performance of bioinformatics pipelines, and they are used in some proficiency testing (PT) activities today.[2]

Compared with hard-to-obtain clinical samples and well-characterized contrived wet lab samples, ISRFs are low cost and can assess a wide variety of variants in a timely fashion.[3] Therefore, some stakeholders are keen to learn more about ISRFs and explore potential opportunities to expand the use of ISRFs in treatment and test development, validation, and quality assurance, especially as treatments target rarer and more complex variants.

In 2022, select stakeholders—including subject matter experts, payers, government agency observers, and others—came together to help launch a working group to explore potential expanded uses of ISRFs in a variety of contexts, given the latest trends in precision medicine research and clinical practice. Following conversations among launch participants and other stakeholders, an initial phase of this work focused on exploring the use of ISRFs in a clinical trial context, and various key stakeholders met virtually in March 2023 to discuss this work.

This *ViewPoints* draws on discussions from the March meeting, along with earlier conversations among stakeholders, and centers on the following topics:

Because this initiative aimed to clarify a potential use case for expanding the application of ISRFs in a rapid, nimble fashion, interviews conducted to date were limited and, as such, this *ViewPoints* should not be mistaken for a comprehensive landscape assessment.

Perspectives on the benefits and drawbacks of ISRFs

Various pathology stakeholders have afforded recent attention to ISRFs and continue to

consider the unique benefits and limitations of ISRF methods. New recommendations published in late 2022 by the AMP and partners highlight the benefits of in silico next-generation sequencing (NGS) datasets and how such datasets are being used today. *Note:* datasets *is the term used in the 2022 recommendations.*[4] *These methods are also referred to in the literature as "in silico mutagenesis of NGS sequence files" or "in silico reference samples;" for the sake of simple, consistent terminology in this* ViewPoints, *we will use "ISRFs" to describe this approach, except in cases where sources refer to in silico data in an explicitly broader or distinct context. Details on the 2022 recommendations are below.* Additionally, the Centers for Disease Control and Clinical Laboratory Improvement Amendment (CLIA) Advisory Committee are working to assess the use of ISRFs to support bioinformatics pipeline validation.[5]

Highlights of the 2022 recommendations by AMP, the Association for Pathology Informatics (API), and the College of American Pathologists (CAP)

The 2022 recommendations, led by key pathology stakeholders, characterize a variety of approaches for generating in silico NGS datasets that can be used to simulate variants and help laboratories assess potential limitations in their assays' bioinformatics. In summary, these recommendations

- focus on employing ISRFs during assay development and validation, while also acknowledging the use of ISRFs in PT today;
- detail a variety of different ISRF methods, each of which can meet specific development, validation, and quality-assurance objectives;
- describe software and third-party vendors who generate ISRFs for laboratories to use;
- emphasize that in silico methods are not a replacement for clinical or well-characterized wet lab sample quality-assurance processes; and
- call for ongoing engagement with vendors and manufacturers to address difficulties around file exchanges and other technical challenges.

The literature and efforts above acknowledge the need for ongoing evaluation of these methods. Indeed, the use of ISRFs has been limited to date: in a laboratory practices survey conducted as part of the 2022 recommendations, only 36% of respondents said they already used ISRFs, "most commonly to test pipeline performance, technical limitations, updates, and assay validation."[6]

Drawing from this landscape of existing work and conversations as part of this working group's

effort, key limitations of ISRFs are frequently described as follows:

- **ISRFs only assess bioinformatics pipeline performance and thus cannot assess the other important preanalytical and analytical steps that a laboratory undertakes when handling a clinical specimen or wet lab reference sample.** In line with the 2022 recommendations, some experts emphasize that ISRFs are only a supplemental tool, not a replacement for patient samples or well-characterized wet lab samples, as is also emphasized by regulators.[7] Some stakeholders underscore regulators' historically cautious perspective toward ISRFs because of these limitations.
- **Some laboratories have limited capacity to seamlessly use ISRFs.** Some ISRF approaches used to assess pipeline performance rely on datasets generated by laboratories' own pipelines, which are sent externally to third parties for mutagenesis and then sent back to participating laboratories.[8] In these cases, some laboratories have had difficulties downloading or finding files within workflows.[9]
- **Because of this limited capacity, implementing an ISRF analysis may require more time and support to execute than some might anticipate.** Workarounds exist to help laboratories with these processes, as evidenced by the relatively large-scale implementation of some in silico-based PT activities.[10] However, these workarounds require expert consultation with laboratory staff customized to each laboratory's needs.[11] This can be a challenge for laboratories facing tight human and economic resourcing constraints and a limited number of in silico experts able to guide them.

> *"We know from experience that about 25% of labs have an extremely hard time doing this, as they really don't have the resources and the expertise. And part of that is due to the way that the Thermo Fisher and Illumina platforms can face some difficulties in importing files that were not generated on that machine for bioinformatics analysis."*
>
> —Technical expert
>
> *"We need to make it easier for labs to do this. Can Illumina make software on this? Can you make it seamless? That would make it more likely to be adopted."*
>
> —Subject matter expert

Despite the caveats of ISRFs, stakeholders also underscore their potential utility and why this utility may be important to tap into now:

- **An ISRF process still likely involves less time and cost than developing wet lab samples.** Such differences in time frame and cost were observed in earlier pilots in this space and are echoed by some experts today. *"Experience has shown that well-characterized wet lab samples can, in practice, take 1.5 years to reach a lab. In silico's benefits, versus wet lab samples, are that they can be deployable in a matter of weeks,"* one expert said.
- **ISRFs provide an opportunity for test developers to create samples in instances where variants are rare and complex.** Because trials and treatments increasingly target narrowly defined populations and more complex variants, there are, as one laboratory professional

noted, *"some interesting applications [for ISRFs], especially for rare variant types that are difficult to source, like fusions,"* and, as other experts noted, complex structural variants.

- **Broadly, there is increasing use of NGS in cancer diagnosis—and, in parallel, increasing interest by laboratories in ISRF methods.** As of 2017, 75% of oncologists reported using NGS to direct treatment for targeted therapies, a number that is likely to have increased substantially over the last few years.[12] Thus, the time is ripe to continue to assess the potential of ISRFs as a supplemental tool for the diagnostic community to support test validation and quality assurance, in line with recent commentary on the fairly successful deployment of ISRFs in PT.[13] Indeed, 46% of respondents in the above-mentioned 2022 survey on laboratory practices said they had not yet used in silico data but were planning to do so, signaling interest from the community in broadening use of ISRFs and the need for education about what ISRFs can and cannot do.[14]

Tapestry Networks launched a multistakeholder in silico working group in September 2022 to explore these issues, with the intention to grow as specific topics were prioritized. Working group participants and other experts discussed a variety of potential areas pertaining to ISRF use to which it may be helpful for the working group to devote time, energy, and resources, to the benefit of the scientific and clinical community. *These focus areas are summarized in Appendix 1 (page 11) and in Tapestry Networks' public report of the launch discussions.*[15] As a result of diverse feedback and various qualitative interviews, the effort first prioritized a deep dive to consider the use of ISRFs for treatments and tests currently under development (i.e., in a premarket, clinical trial environment) while simultaneously laying the groundwork for understanding what can be done to potentially make ISRFs easier for laboratories to use.

Exploring a use case for ISRFs during clinical trials

Building upon the insights above and given the initial focus direction of the working group, stakeholders convened in March 2023 to consider the value of employing ISRFs in a clinical trial context as the use of diverse assays and laboratories in trials becomes more common. They discussed what incentives might prompt the utilization of ISRFs in ways that would yield benefits for trial sponsors, laboratory partners, patients, and other stakeholders, and they learned about the potential benefits and complexities involved in an ISRF process. Key takeaways from the meeting are described below.

Trials employing local testing are complex and require new approaches to ensure assay performance

Clinical trial design is evolving rapidly. In oncology, trial sponsors and site investigator partners are increasingly interested in using multiple clinical trial assays (CTAs) or distributed laboratory networks to enroll diverse groups of patients onto trials quickly.[16] Trial sponsors have both pragmatic and altruistic interests in doing so. *"From a patient access perspective, it's absolutely the right thing to do. You have a result from the lab, and you want to qualify a*

patient for enrollment. Why should we ask for a re-biopsy? How can we justify this? There is in part an altruistic motivation: getting patients onto a trial in a timely manner," one sponsor said.

There are various situations in which a local-testing trial design might be advantageous to trial sponsors and other stakeholders. *For detail, please see the text box below.*

The rationale for local testing

Thought leaders have recently given attention to greater use of local assays during clinical trials, especially for treatments targeting rare biomarkers for which obtaining a certain volume of patients in a timely fashion is challenging under traditional paradigms (i.e., one central laboratory test for enrollment).[17] During the March meeting, as context for the conversation on ISRFs, trial sponsors expanded on the rationale for local testing under certain conditions:

- **Instances in which patients face a poor prognosis and/or resampling them is a gross inconvenience.** In such circumstances, a trial design with local testing is frequently encouraged by site investigators and may involve situations where relevant tests are already standard of care. One sponsor detailed a situation that reflects these factors and warrants a local-testing approach: *"For an [acute myeloid leukemia] study, we have to enroll based on TP53 [mutations]. Patients have already been tested—it's part of the standard of care; it's [National Comprehensive Cancer Network] guidelines. We still require a companion diagnostic, but in this case, if we were to do this in a standard way, we would have to get them retested. That time frame—even though we can do this quite rapidly, still within six to eight days—is not something that investigators want to wait for because these patients have a poor prognosis. That's a very clear use case."*
- **Unique trials where a distributed laboratory network is built into a trial's design, (e.g., broad-based basket trials).** The National Cancer Institute's (NCI's) efforts in this space are particularly relevant. NCI's ComboMATCH trial will be able to leverage its prior NCI Match Designated Qualified Laboratory Network—which includes laboratories that were qualified during the original MATCH trials—for ComboMATCH, as well as a group of laboratories comprising NCI's Molecular Diagnostic Network.[18]
- **As a complementary approach to, and not a replacement for, traditional companion diagnostic development processes—at least in the view of some trial sponsors.** That said, others suggested that traditional in vitro and companion diagnostic development processes may need to evolve as well, while recognizing that such issues were outside the scope of the March discussion.

Relevant stakeholders emphasized at the meeting that despite their benefits, such trials add complexity and risk for trial sponsors. Indeed, trial sponsors must ensure the performance of all assays used during a given trial, per FDA guidance:

> If multiple testing sites are used (e.g., use of regional test centers or testing in different countries), a single testing protocol should be used at all sites. To assure that results are not affected by site of testing, FDA recommends that the sponsor evaluate comparability of test results among potential sites prior to initiating trial testing at those sites. This can be achieved through a site qualification scheme or other mechanism. The use of multiple assay protocols, different technologies or a method that lacks reproducibility across labs could result in variable test performance and lack of comparability among test results.[19]

There is thus, as one participant noted, a *"huge interest in making sure [trial sponsors] enroll the right patients,"* but no explicit guidance pertaining to how a sponsor should evaluate comparability of the assays used to do so. Therefore, some stakeholders involved in these kinds of clinical trials report various ways in which sponsors are developing operational steps to ensure that diverse CTAs employed during a trial are identifying the right patients. Such activities may comprise a site qualification scheme in which sponsors ask for test validation data and/or ask laboratories to demonstrate the performance of their assays via well-characterized reference samples. According to a trial sponsor, this involves a *"ton of work"* but is *"doable."*

Some participants asked if trial sponsors could rely on existing certification criteria (i.e., CLIA and CAP certification) instead of undertaking additional steps. Trial sponsors noted that such certifications are a starting point, but the FDA has signaled to date that certifications alone are not sufficient for trial data submission. These also may not be relevant in the context of large-scale global trials. The onus thus lies with trial sponsors to conduct qualification measures.

ISRFs may meet the market need for economical reference samples—with caveats

Within the above context, stakeholders affirmed that there is significant market need for high-quality reference samples to support trial sponsors in ensuring the performance of assays in trials that employ local testing, especially in oncology for somatic mutations. Some see ISRFs as being a potentially helpful, economical, and complementary reference sample tool to help trial sponsors gain confidence in laboratories' bioinformatics. Meeting participants discussed how deploying an ISRF process during a trial comes with both potential benefits and trade-offs.

Use of ISRFs for rare and complex variants is promising but still emerging

One participant said he saw the greatest potential for ISRFs in their ability to mimic complex or rare structural variants and/or variants not frequently seen in clinical samples: *"I think if ISRF materials are going to be helpful, they probably have to be used for challenging variants. One variant class that we did not assess [for our trial] was fusions. It just was very complicated for us to source appropriate materials because they're so rare. I think that's where maybe the most opportunity is."* Practical implementation of ISRF processes for complex, rare biomarkers has, however, been more limited than the use of ISRFs to assess single nucleotide variants and small indels, which has been well established.[20] Some also opined that developing ISRFs for more complex variants may be technically challenging.

> *"Take microsatellite instability. You can design an algorithm to model anything. The question is, What is it that the client really wants? How have they defined MSI? What is their capture region?"*
>
> —Technical expert

Others emphasized that ISRFs are not well established for more complex variants because there has been minimal relevant demand to date—not because of unsolvable technical complications: *"Nobody is doing it because nobody has asked."* Furthermore, some experts noted that those requesting ISRFs would benefit from considering specific questions they seek to answer about pipeline performance from an ISRF process to help focus file development.

The customized ISRF process has pros and cons

In describing how an optimal ISRF process works to stakeholders at the March meeting, experts underscored that ISRFs are customized for each participating laboratory and set of variants. *"An individual laboratory will take a reference sample, usually a cell line sequence in the assay that they're using for a clinical trial or in routine clinical practice, and they would do the nucleic acid extraction, make a library, and then sequence that. Then they would send it to an intermediate group that would do the mutagenesis, and that intermediate group then would insert mutations into those sequence reads, and then those mutagenized files are then sent back to the laboratory,"* one expert said.

Several participants emphasized the value of this approach, which mimics how each laboratory's pipeline would respond to a real sample and therefore can solicit highly individualized insights about pipeline performance. In contrast, generic mutagenized files are, in the view of some experts, nearly meaningless, except in cases where a group of laboratories are using the same off-the-shelf in vitro diagnostic kit. The principle of customization is also in line with some trial sponsors' expectations, whereby ISRFs might be created and deployed in a trial-specific fashion (i.e., enabling analysis of relevant biomarkers for a given trial).

> *"In silico approaches where you utilize a standard set of files that you then distribute to a group of laboratories isn't a model that captures what individual labs do."*
>
> —Technical expert

For some, customization raises operational and scalability questions. The number of data files exchanged across laboratories and steps required for laboratories to undergo an ISRF process were of particular concern to some trial sponsors. Some asked whether the process could be further simplified through use of patient samples that a laboratory already sequenced in place of cell lines, but others noted that the exchange of patient-derived genomic data without relevant permissions in place may violate Health Insurance Portability and Accountability Act laws. In response to these concerns, some experts were confident that the two-step upload and download process should not present a major problem for most laboratories, as it entails only one additional step beyond a more generic ISRF process (e.g., those that may be employed for laboratories using kits).

Determining the optimal place for ISRFs within the trial workflow requires more attention

Understanding where an ISRF process should be implemented within a local-testing trial workflow is likely to require ongoing discussion among stakeholders, as participants in the March meeting saw value in several options. Because trial sponsors involved in local testing-based trials are likely to do several upfront qualification activities (e.g., review of validation data), some noted that the most valuable role for ISRFs may instead lie in helping sponsors monitor assay performance over the duration of a trial to account for test updates. Some pointed to relevant trial examples where the FDA has requested ongoing monitoring of participating laboratories.

Others noted that ISRFs could simply complement other site qualification activities during an upfront qualification process and offer a targeted focus on laboratories' bioinformatics. Finally, some saw value (if regulators were to support it) in the potential use of ISRFs as a standalone process that could replace other site qualification activities. *"If you assess the value of the information you can get about an individual pipeline with ISRFs, you get good bang for your buck,"* one participant said.

Developing a sustainable ISRF approach for trials will likely require precompetitive, collaborative forums and leadership

Some stakeholders wondered whether trial sponsors in the biopharmaceutical industry should be implementing such efforts unilaterally with preferred vendors or whether existing organizations that provide PT services should play a role in collaborating with industry to advance the use of ISRFs during trials. Similarly, even if industry players moved forward with an ISRF process on an individual basis, others asked if precompetitive entities or platforms could serve as forums to identify laboratories that successfully underwent an intensive site qualification and/or ISRF-related process for certain types of biomarkers. Such forums—or even a public listing of laboratories that underwent such a process—might mitigate against a situation where laboratories would be compelled to demonstrate the performance of their assay for the same or similar biomarkers multiple times. *"Can industry get together on this in a*

consortia? Can we say, precompetitively, 'This is how we will approach this'? We have to ensure quality via a regulated approach, but it can't be super onerous," one participant said.

Application of ISRFs may be tied to ongoing dominance of specific platforms

Most ISRFs today are designed to assess bioinformatic pipeline performance on platforms manufactured by the two main sequencing platform market leaders: Illumina and Thermo Fisher. These platforms are, however, evolving rapidly, becoming more complex and fragmented, and facing potential market competition, as some stakeholders noted. This raises questions about the sustainability and scalability of current ISRF approaches. One subject matter expert said, *"We will face increasing fragmentation in this space. It's really easy to create reference material for a couple of Illumina [sequencer types], but if you want to go beyond that, the hill to climb is going to become much, much steeper."* Another recognized this as a concern, but given the persistent dominance of the two leading platforms, did not emphasize it as an immediate challenge: *"I don't know if I quite lay awake in bed at night worried about this, though it does raise some issues about what this clinical space is going to look like three to five years from now."* Instead, they underscored that *"you've got to start somewhere."*

Conclusions and the way forward

Despite the above complexities, some participants remained optimistic about continuing to explore the use of ISRFs for trials. One noted, *"We can all come up with limitations of in silico, but we either do that or nothing."* Some trial sponsors also emphasized the importance of a rigorous qualification process during trials more broadly, pointing to the fact that trial-based qualification activities may strengthen testing in a postmarket, clinical context. One said, *"We're proactively saying we're going to use multiple CTAs in this study and we're going to ensure quality, however we do this—whether it be through in silico files, wet lab proficiency samples or a combination. When we do that upfront, it's better not only for patients but also for us in the commercial setting, where we actually feel more confident that the laboratories we use to enroll in our trial are actually testing patients and using quality methods."*

> *"Samples are limited, and any progress we can make on getting comparable results is something we should try for."*
>
> —Subject matter expert

Many agreed that to resolve these challenges, there is a need for greater multistakeholder collaboration to create available reference samples—including ISRFs—to support clinical trials that employ local testing and thus expand patient enrollment. With this vision in mind, some stakeholders discussed specific next steps during and immediately after the meeting:

- **Advance the use of ISRFs during trials.** Some stakeholders were keen to develop a general approach to using ISRFs during trials, including potentially piloting doing so. Such an approach would rest on further discussion about the areas within the trial workflow (i.e.,

upfront/complementary or standalone process for ongoing monitoring) and the types of variants for which an ISRF process would offer the most value.

- **Develop an overarching framework for trials that use local testing.** Such a framework would build from prior work in this space and would need to emphasize both practical considerations and the need for high standards to meet FDA requirements. For those favoring this approach, ISRF application may be part of such a framework but not a standalone focus. In this case, some specifically asked whether industry could look to prior and/or existing examples of local-testing trials (e.g., NCI ComboMATCH) and, based on those, develop consensus-based principles and standards for the broader community for such trials moving forward.

Following publication of this *ViewPoints*, Tapestry Networks and supporters of this effort will continue to discuss potential opportunities to pilot some of the approaches discussed at the March meeting in specific trials and consider whether such pilots would necessitate multistakeholder, precompetitive collaboration with the broader community.

About this document

This *ViewPoints* reflects the use of a modified version of the Chatham House Rule whereby comments are not attributed to individuals, corporations, or institutions. Comments by working group and meeting participants and other stakeholders appear in italics.

Tapestry Networks is a privately held professional-services firm. Its mission is to advance society's ability to govern and lead across the borders of sector, geography, and constituency. To do this, Tapestry forms multistakeholder collaborations that embrace the public and private sector, as well as civil society. The participants in these initiatives are leaders drawn from key stakeholder organizations who realize the status quo is neither desirable nor sustainable and are seeking a goal that transcends their own interests and benefits everyone. Tapestry has used this approach to address critical and complex challenges in corporate governance, financial services, and healthcare.

Appendix 1: Potential focus areas for an ISRF working group

A multistakeholder in silico working group was launched in September 2022 to explore opportunities for ISRFs to support high-quality treatment development and test validation and quality assurance. Stakeholders involved in the working group and other experts considered several potential areas pertaining to ISRF application for an initial focus of this effort:[21]

- **Use of ISRFs during trials in which biopharmaceutical companies are enrolling patients based on a diversity of laboratory assays.** Stakeholders such as Friends of Cancer Research have discussed greater use of diverse local laboratories and multiple CTAs during treatment development, especially for treatments targeting rare biomarkers.[22] In these situations, stakeholders may need to think differently about approaches to assess and compare performance of assays used to identify patient populations and enroll them in treatment based on their biomarker status. In concept, ISRFs could serve as a complementary tool to help accomplish these aims.
- **For assays already in use, assessing the role of payers in creating incentives for laboratories to consider enhanced quality-assurance approaches, including ISRF-based ones.** This approach has been recently reported in the media.[23] Others disagree with a payer-led approach, emphasizing that evolving quality-assurance processes—including through the use of approaches like ISRFs—need to be led by the laboratory community and/or regulators.
- **Other areas that could be addressed in an initial phase of work**. These include an exploration of technical bottlenecks with ISRFs, namely the difficulties laboratories and platforms have with recognizing and exchanging these files. Launch participants also raised the idea of doing a more comprehensive, broad-based landscape assessment of all possible ISRF use cases as an initial project.

To prioritize specific focus activities from the above ideas for an initial output, Tapestry conducted a follow-up survey of launch participants and select additional qualitative interviews, both of which yielded stakeholders' considerations on practicality, scope, timing, and resourcing for an exploration of ISRFs.

As a result of these discussions and as addressed in this *ViewPoints*, a use case focusing on ISRF deployment during clinical trials was the first output of the working group, with other potential outputs to be determined based on stakeholder interest and available resources.

Appendix 2: Contributors

The following stakeholders provided perspectives on these topics during interviews in 2021, 2022, and early 2023, both in the context of launching the working group and the clinical trial use case.

- **Abbott:** Kathryn Becker, Director Licensing & Acquisitions
- **Arnold Ventures:** Katherine Szarama, Director, Drug Pricing (formerly at Emerson Collective and CMS)*
- **Blue Cross Blue Shield Association:** Naomi Aronson, Executive Director, Clinical Evaluation, Innovation, and Policy; Judy Mouchawar, Medical Director*
- **Broad Institute:** Niall Lennon, Chief Scientific Officer of the Broad Institute's clinical laboratory, CRSP
- **Center for Genomic Interpretation:** Maria Clark, Principal Scientist; Julie Eggington, Cofounder and CEO; Heather King, Director of Customer Success
- **Centers for Disease Control and Prevention:** Lisa Kalman, Health Scientist*
- **Cincinnati Children's Hospital Medical Center:** Somak Roy, Associate Professor and Director of Molecular Pathology*
- **Emory University School of Medicine:** Barbara Zehnbauer, Adjunct Professor of Pathology*
- **eviCore:** Lon Castle, CMO, Laboratory and Specialty Drug Services
- **Friends of Cancer Research:** Jeff Allen, President and CEO;* Mark Stewart, Vice President, Science Policy;* Hillary Stires, Science Policy Analyst*
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- **Massachusetts General Hospital:** Keith Flaherty, Director of Clinical Research, Mass General Cancer Center
- **Medical Device Innovation Consortium:** Pamela Goldberg, former President and CEO; Maryellen de Mars, Program Director, Clinical Diagnostics; Joseph Sapiente, Vice President, Clinical Science and Technology
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- **National Cancer Institute, National Institutes of Health:** Chris Karlovich, Associate Director, Molecular Characterization Laboratory at the Frederick National Laboratory for Cancer Research;* Lisa Meier McShane, Associate Director, Division of Cancer Treatment & Diagnosis, and Chief, Biometric Research Program*
- **National Institute of Standards & Technology:** Justin Zook, Co-Leader, Biomarker and Genomics Sciences Group*
- **Nucleai:** Ken Bloom, Head of Pathology (formerly at Konica Minolta)
- **PLUGS® (Patient-centered Laboratory Utilization Guidance Services):** Mike Astion, Co-founder

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- **Strata Oncology:** Dan Rhodes, Co-founder and CEO
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- **Washington University School of Medicine:** John Pfeifer, Professor, Pathology and Immunology, and former Quality Pilot Scientific Technical Working Group Chair*

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Endnotes

[1] Eric J. Duncavage et al., "Recommendations for the Use of *in Silico* Approaches for Next-Generation Sequencing Bioinformatic Pipeline Validation: A Joint Report of the Association for Molecular Pathology, Association for Pathology Informatics, and College of American Pathologists," *Journal of Molecular Diagnostics* 25, no. 1 (October 2022).

[2] Larissa V. Furtado et al., "Four-Year Laboratory Performance of the First College of American Pathologists In Silico Next-Generation Sequencing Bioinformatics Proficiency Testing Surveys," *Archives of Pathology and Laboratory Medicine* 147 (February 2023), 137–142.

[3] John D. Pfeifer et al., "Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics," *American Journal of Clinical Pathology* 157, no. 4 (April 2022), 628–638; Eric J. Duncavage, Haley J. Abel, and John D. Pfeifer, *"In Silico* Proficiency Testing for Clinical Next-Generation Sequencing," *Journal of Molecular Diagnostics* 19, no.1 (January 2017), 40.

[4] Duncavage et al., "Recommendations for the Use of *in Silico* Approaches for Next-Generation Sequencing Bioinformatic Pipeline Validation."

[5] Lisa V. Kalman and Ira M. Lubin, "New CDC Partnerships to Advance the Development and Validation of Next Generation Sequencing Tests: A Publicly Available List of Expert Curated Variants," *Genomics and Precision Health* (blog), November 16, 2021.

[6] Duncavage et al., "Recommendations for the Use of *in Silico* Approaches for Next-Generation Sequencing Bioinformatic Pipeline Validation," 20.

[7] US Food and Drug Administration, *Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)–Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases: Guidance for Stakeholders and Food and Drug Administration Staff* (Washington, DC: Food and Drug Administration, 2018), 24; and Duncavage et al., 17–18.

[8] Duncavage et al.

[9] Pfeifer et al., "Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics," 632, 635; and Duncavage et al., 20.

[10] Furtado et al., "Four-Year Laboratory Performance of the First College of American Pathologists In Silico Next-Generation Sequencing Bioinformatics Proficiency Testing Surveys," 142.

[11] Pfeifer et al., 632, 635.

[12] Andrew N. Freedman et al., "Use of Next-Generation Sequencing Tests to Guide Cancer Treatment: Results from a Nationally Representative Survey of Oncologists in the United States," *JCO Precision Oncology* (November 13, 2018).

[13] Furtado et al., "Four-Year Laboratory Performance of the First College of American Pathologists In Silico Next-Generation Sequencing Bioinformatics Proficiency Testing Surveys."

[14] Duncavage et al., 20.

[15] Working Group on In-Silico Reference Files, *Launching a Working Group to Explore Expanded Use of In-Silico Reference Files in Molecular Diagnostics* (Waltham, MA: Tapestry Networks, 2022).

[16] Imein Bousnina et al., *Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications* (Friends of Cancer Research, 2022); Funda Meric-Bernstam et al., "National Cancer Institute Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH)," *Clinical Cancer Research* 29, no. 8 (April 2023), 1412–1422.

[17] Bousnina et al., *Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications.*

[18] Meric-Bernstam et al., "National Cancer Institute Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH)."

[19] Center for Devices and Radiological Health, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product: Draft Guidance for Industry and Food and Drug Administration Staff (draft guidance)* (US Food and Drug Administration, July 15, 2016).

[20] Duncavage et al.

[21] For more detail, see Tapestry's public report from the September 2022 launch discussions: Working Group on In-Silico Reference Files, *Launching a Working Group to Explore Expanded Use of In-Silico Reference Files in Molecular Diagnostics.*

[22] Bousnina et al., *Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications.*

[23] Turna Ray, "Highmark Asks Labs for Additional Validation Data on Cancer NGS Tests; Will Other Insurers Follow?" *Precision Oncology News*, October 3, 2022; Turna Ray, "Nonprofit's Efforts with Payors to Assess NGS Labs' Variant Interpretations Spark Debate," *Precision Oncology News*, October 4, 2022.