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ACMG STATEMENT

Points to consider for the reporting of variants of uncertain significance in germline genetic and genomic testing: A statement of the American College of Medical Genetics and Genomics (ACMG)

Chloe Mighton[1,2], Aya Abu-El-Haija[3,4], Vimla Aggarwal[5], Yassmine M.N. Akkari[6,7], Caroline Astbury[8], D. Hunter Best[9,10], Laura K. Conlin[11], Steven M. Harrison[12], Nan Jiang[13], Paul Kruszka[14], Dianalee McKnight[15], Tiffany T. Nguyen Dolphyn[16], Farid Barquet Ramos[17], Christie P. Thomas[18], Lora J.H. Bean[19], Heidi L. Rehm[1,2,3]; on behalf of the Laboratory Quality Assurance Committee[20,*]

Disclaimer: This Points to Consider document is designed primarily as an educational resource for clinical laboratory geneticists to help them provide quality clinical laboratory genetic services. Adherence to these Points to Consider is voluntary and does not necessarily assure a successful medical outcome. These Points to Consider should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinical laboratory geneticists should apply their own professional judgment to the specific circumstances presented by the individual patient or specimen.
Clinical laboratory geneticists are encouraged to document in the patient's record the rationale for the use of a particular procedure or test, whether or not it is in conformance with these Points to Consider. They also are advised to take notice of the date this document was adopted, and to consider other relevant medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures. Where individual authors are listed, the views expressed may not reflect those of authors' employers or affiliated institutions.

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Introduction

Genetic testing has become a powerful diagnostic tool in many aspects of medical practice. It can provide information regarding the genetic etiology for individuals manifesting symptoms, inform carrier status and recurrence risk for genetic disorders, enable population-based screening for disease risk, and guide therapy to optimize outcome and avoid adverse treatment sequelae. Although guidelines have been established for the classification of sequence and structural variants into categories including pathogenic (P), likely pathogenic (LP), uncertain significance (VUS), likely benign (LB), and benign (B),[1,2] limited professional

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*Correspondence: ACMG. *Email address:* documents@acmg.net
Affiliations are at the end of the document.

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guidance has been put forth on when to report VUS and whether it should vary based on specific types of tests and indications.

Clinicians and laboratory professionals understand the potential impacts of returning VUS on both the providers and the individuals/families undergoing testing. VUS can cause concerns for the individual undergoing testing,[3-7] uncertainty for clinicians,[8-10] as well as incur significant resources in follow-up or even lead to inappropriate medical care when misinterpreted as causal[3,11,12] or dismissed as irrelevant. As such, it is important to carefully weigh the benefits and drawbacks of reporting VUS in various clinical settings.

Historically, VUS have been returned in settings where there is a high prior probability of obtaining a positive result or high likelihood that a novel variant may be deemed causal. These include testing of symptomatic individuals (Box 1) with a strong suspicion for a causal genetic variant to be identified (eg, multigene panel testing in an individual with retinitis pigmentosa or hypertrophic cardiomyopathy) or cytogenomic results impacting multiple genes in large chromosomal regions. In these cases, the benefit of returning a VUS is that investigations could be undertaken, such as building evidence, that might move a variant from VUS toward pathogenic or benign and thus clarify causality.[13] Returning a VUS in these settings is also important, given that a large fraction of causal variation is unique to a single family and building evidence may only be possible if the variant is returned at initial identification. Indeed, 78% of the over 4 million unique variants in ClinVar have been submitted by a single laboratory suggesting most are probably observed in a single individual (ClinVar. https://www.ncbi.nlm.nih.gov/clinvar/, Accessed January 2026). Examples of follow-up to build evidence may include (1) parental testing to determine de novo occurrence or phasing of 2 sequence variants, (2) segregation testing in affected and unaffected family members,[14] (3) RNA analysis for aberrant splicing,[15,16] (4) methylation analysis, (5) enzyme analysis or expression assays to identify expected histological or functional results, (6) collaborations with researchers performing targeted functional assays,[17-19] or (7) data sharing[20-22] to aggregate multiple observations.[23,24]

In contrast to these settings where VUS are often returned, in most asymptomatic testing (Box 1) situations in which individuals are not being tested because of symptoms or a family history of genetic disease, the return of VUS is generally not recommended.[25] For example, the American College of Medical Genetics and Genomics (ACMG) working group on the return of secondary findings recommends returning only P/LP variants.[26] On the other hand, an exception has been made for partner-based carrier screening, in which VUS can be returned when found in a gene for which the partner has a P/LP variant in the same gene.[27] In this scenario, in the absence of phenotype or family history, the VUS does not have a higher prior probability of pathogenicity compared with any other VUS found in the general population; however, the low rate of couples receiving carrier results in the same gene, as well as the potential for offering additional clinical and genetic prenatal screening, may form a reasonable basis for VUS return.

Box 1 Definitions

Symptomatic testing: Symptomatic testing refers to genetic or genomic testing that is initiated based on an individual's signs or symptoms of disease. In symptomatic testing, there is a higher prior probability of obtaining a positive result compared with asymptomatic testing.

Asymptomatic testing: Asymptomatic testing refers to genetic or genomic testing that is performed in the absence of signs or symptoms of disease. In asymptomatic testing, detected variants have a lower prior probability of pathogenicity, unless there is a family history of a genetic disease.

Although the approaches outlined above are generally accepted as best practices, as genetic testing has gained much wider adoption, more strain has been placed on laboratories and clinicians to manage returned VUS. For example, as the content and phenotype spectrum of multigene panels have expanded (eg, a broad neurodevelopmental panel vs a focused epilepsy panel or a broad cardiac panel vs a focused arrhythmia panel), a much higher rate of VUS are being returned, with roughly 33% of multigene panel reports including VUS.[28] In addition, underrepresented genetic ancestry groups have been observed to have a higher rate of VUS because of a lack of ancestry-matched population data, as well as fewer clinical studies focused on diagnosis in these populations.[29,30] In addition, it is now recognized that most sequence and structural VUS that are reclassified are downgraded toward B/LB over time (75% to 95% of reclassified VUS) as opposed to moving to P/LP,[13,14,31-36] suggesting that most efforts to build VUS evidence will not lead to identification of a causal variant.

One approach to help alleviate this burden is the subdivision of VUS into distinct subclasses, including VUS-low (the lowest level of pathogenic evidence within the VUS range), VUS-mid (equivocal level of evidence of pathogenicity), and VUS-high (upper fraction of VUS that borders LP), allowing clinicians the ability to target their clinical management only to certain subclasses. The current ACMG/AMP guidelines for variant classification allow the use of additional subclasses,[1] which can help further subdivide VUS that currently have a wide range of probability for causality from 10% to 90%. The current UK guidelines for variant classification also recommend the use of subtiers for internal tracking purposes.[37] Several laboratories have long-standing experience with VUS subclasses and have demonstrated that the rate of reclassification is distinct across sub-tiers.[38] In addition, one laboratory has used subclasses to remove VUS-low from multigene panel test reporting in hereditary cancer testing, and another has used

subclasses to only report VUS-high in a population screening study.[39] Furthermore, specific guidance will be provided in the upcoming revised standards for variant classification (SVCv4.0) on how to subdivide VUS based on a point system and will provide standardized terms and evidence levels for these subclasses (VUS-low, VUS-mid, and VUS-high), both of which will ease adoption of these approaches in laboratory practice.

Although some standards and norms exist for guiding VUS reporting, a unified and systematic approach is still lacking, especially in relation to the upcoming VUS subclass guidance and the fact that many laboratories already use VUS subclasses but with laboratory-specific approaches. In this Points to Consider document, our goal is to explore a variety of settings and provide basic guidance for the reporting of germline VUS for both sequence and structural variants, as well as highlight areas where more research is needed to inform future practice. Although this document provides guidance on the reporting of VUS subclasses, more detailed guidance on the generation and naming of VUS subclasses will be covered in the forthcoming sequence variant classification standards.

Materials and Methods

Working group members included clinical laboratory geneticists (with expertise in molecular genetics and cytogenetics), medical geneticists, genetic counselors, a genetic nephrologist, and one trainee. The working group held monthly meetings to develop the recommendations. Early meetings included presentations from members of the committee and external experts on approaches to current VUS reporting and related research, to guide the committee's deliberations. Pharmacogenomic experts affiliated with CPIC/PharmGKB were engaged for recommendations related to this area of testing. The working group also collected and reviewed current professional practice policies, technical standards, and research studies, which are referenced throughout this document.

A survey was then developed to seek community input to inform the recommendations. The survey queried respondents about the recommendations being considered by the working group, with Likert response options (Strongly Agree, Agree, Neutral, Disagree, Strongly Disagree). Free-text fields were also included to report additional considerations, suggestions, or concerns. The survey was circulated by the following professional organizations and patient advocacy groups: ACMG, National Society of Genetic Counselors, American Board of Genetic Counseling, American Cytogenomics Conference Listserv, Global Alliance for Genomics and Health, European Molecular Genetics Quality Network, Canadian College of Medical Geneticists, Canadian Association of Genetic Counselors, the Association for Clinical Genomic Science, the International Society of Prenatal Diagnosis, Global Genes, and Rare as One. The survey was open from June to November 2024.

Survey responses for each question were quantified overall and also broken down by profession (eg, laboratory genetics staff, clinicians [physicians and genetic counselors], and patient representatives [patients and patient advocacy organization staff]) and by country of practice, including United States vs non-United States. The working group also reviewed 393 free-text responses, categorized them thematically, and identified considerations or concerns to be addressed in the document. Full survey questions and data can be found in the supplemental material (Supplemental Files 1 and 2). Free-text responses are not included to maintain the anonymity of survey respondents, though the total free-text responses per thematic area were quantified.

Results

Summary of survey findings on the reporting of VUS

The survey was completed by 828 respondents (Figure 1). Respondents were located in 43 countries, most commonly the United States (62.1% [514]), Canada (10.7% [89]), and the United Kingdom (5.6% [46]). Overall, 47.5% (393) were clinicians (physicians or genetic counselors), 41.8% (346) were genetic laboratory directors or other staff, 4.3% (36) were patients/patient advocates/patient organization staff, and 6.4% (53) were from other medical professions. Respondents most frequently endorsed germline genetics as their area of focus (46.3% [383]), followed by pediatrics (45.0% [372]), adult genetics (40.0% [331]), and hereditary cancer (36.7% [304]).

The survey responses largely demonstrated agreement with our proposed recommendations as delineated below (Figure 2). The majority of respondents selected agree/strongly agree regarding our recommendations for whether VUS should or should not be reported in almost all testing scenarios (Supplemental File 1). Only 1 testing scenario had fewer than 50% of respondents endorsing agree/strongly agree; this was a proposed recommendation that laboratories should not return VUS in postnatal germline cytogenomic microarray testing, if unrelated to symptoms or family history. Only 46.2% of respondents selected agree/strongly agree, with the remainder selecting neutral (20.3%) or disagree/strongly disagree (33.5%). Across all testing scenarios, there was some variation in responses based on location of practice and professional role (Supplemental File 1). Notably, patients/patient advocates/patient organization staff generally favored reporting VUS in more scenarios than did clinicians or laboratory staff.

With regard to VUS-high reporting, fewer than 50% of the survey respondents endorsed reporting VUS-high in the setting of secondary/incidental findings, population screening, newborn screening in the absence of correlated clinical/metabolic findings, pharmacogenomic testing in the absence of adverse or unexpected drug response, carrier

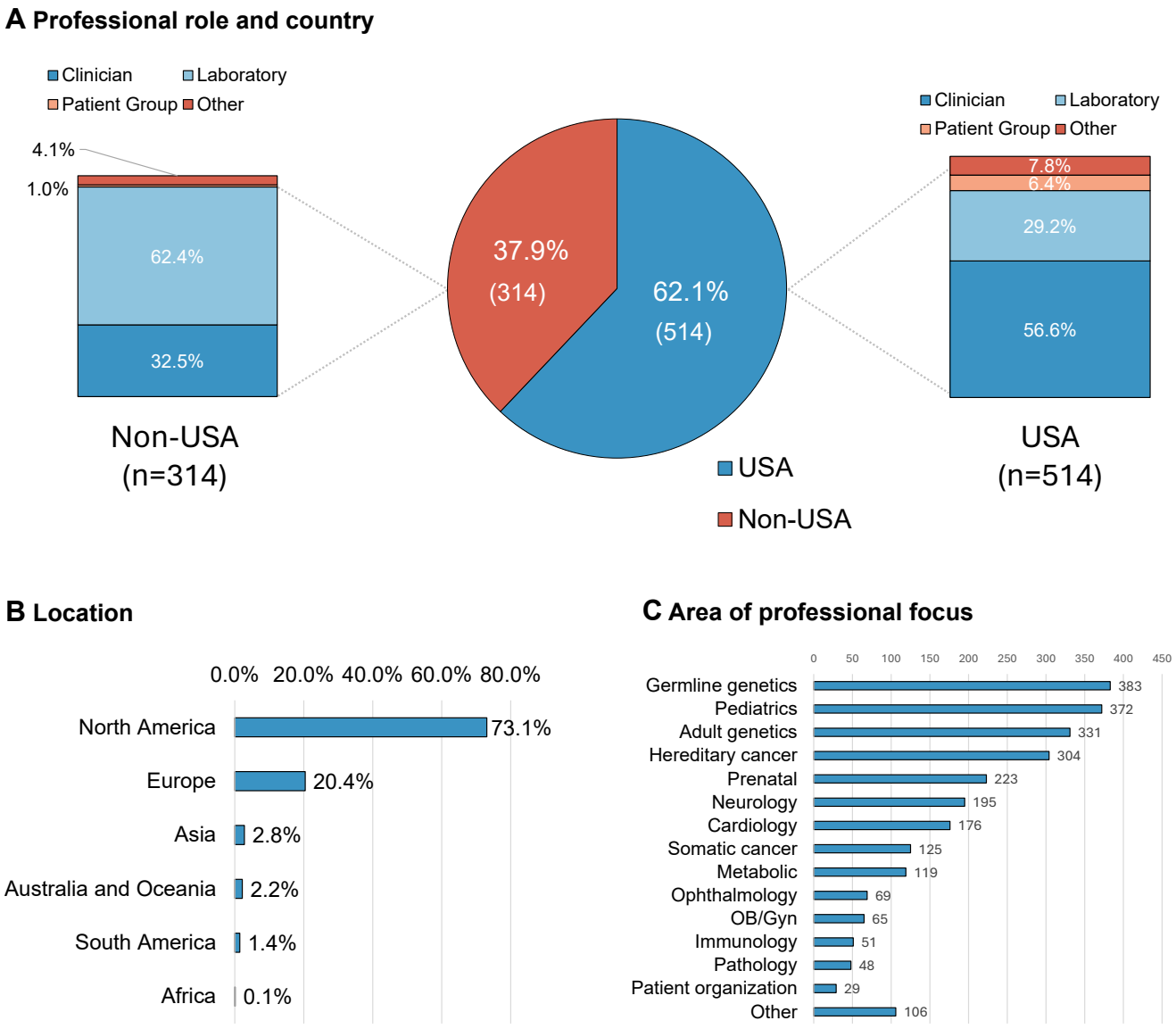

Figure 1 **Survey respondents' characteristics.** Characteristics of survey respondents are classified according to (A) professional role and country, (B) respondent location, and (C) area of professional focus.

screening on a single individual, prenatal testing when unrelated to the phenotype or family history, or when identified as a single heterozygous variant in a gene related to autosomal recessive disease (Supplemental File 1). This is aligned with our recommendations that VUS-high should generally not be reported in these settings, with some possible exceptions as described below.

With regard to strategies for de-emphasizing VUS that are less likely to explain the indication for testing, partitioning VUS and including VUS subclass terms on the report had the strongest support (>60% of respondents). Respondents predominantly felt that the individual undergoing testing should not be provided the option to opt out of having VUS reported. There were quite varied opinions on whether reclassifications between VUS subclasses should be reported, and on whether reclassifications between P and LP should be reported. There was also no clear consensus on whether the principles for reporting VUS in clinical testing should apply to the research setting.

Three hundred ninety-three (393) respondents answered 1 or more of the free-text questions, for a total of 939 free-text responses that were then classified into discrete categories to determine follow-up and area of relevance. About half of the responses (52.8% [496]) were categorized as "No follow-up needed" (eg, comments related to the survey itself or points already addressed by the working group). The remaining 443 were classified as implementation concerns (34.3% [152]), test/result-specific considerations (26.9% [119]), general pushback (19.4% [86]), other context considerations (12.9% [57]), equity considerations (4.3% [19]), jurisdictional differences (3.2% [14]), technology-specific considerations (1.8% [8]), and rare

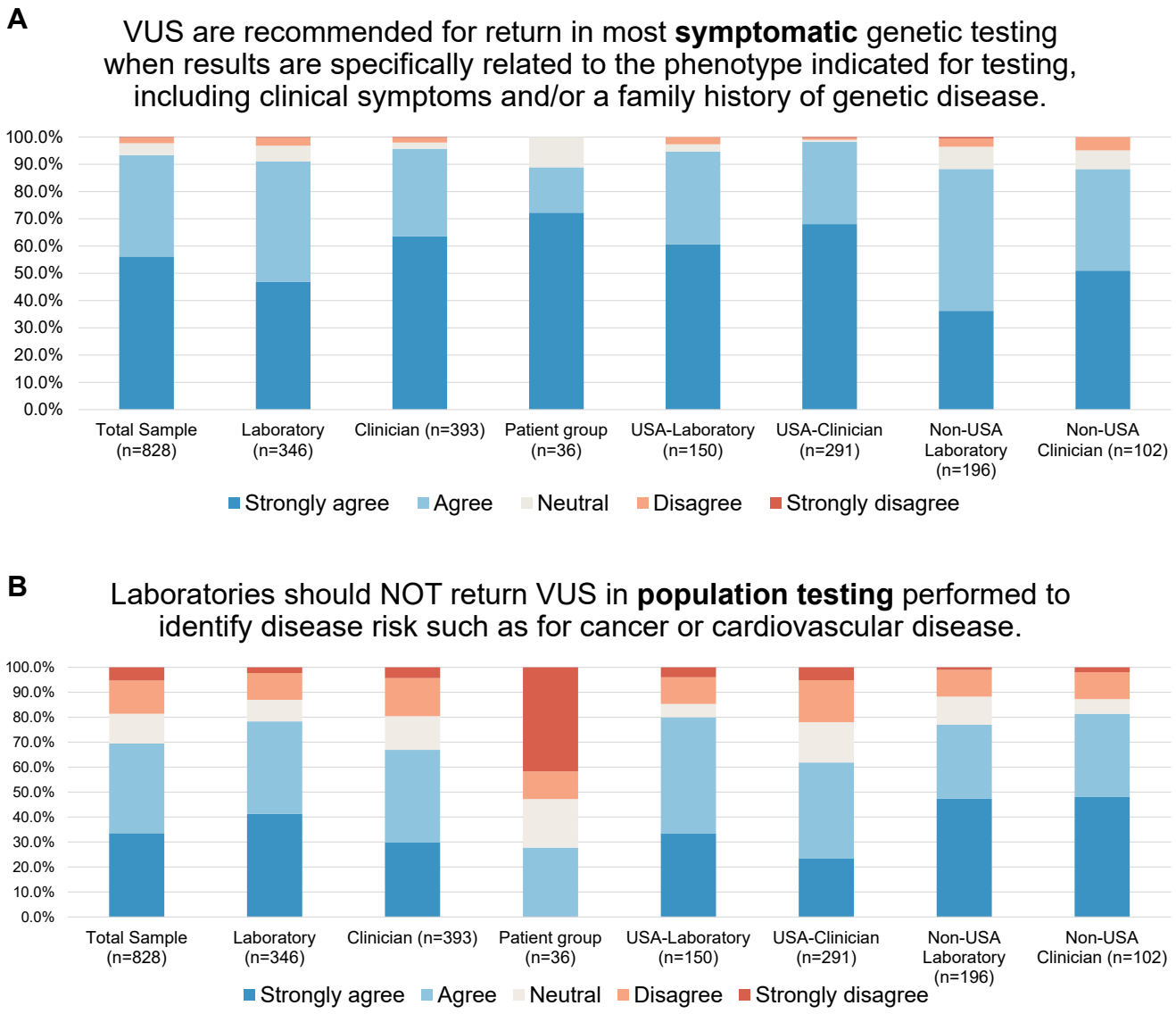

Figure 2 Responses for selected survey questions for the total survey sample, and for subgroups based on professional role and location. Laboratory respondents include laboratory geneticists and variant scientists. Clinician respondents include medical geneticists, genetic counselors, and nongeneticist physicians. Patient group respondents include patients and representatives from patient organizations. A. Responses related to return of VUS in symptomatic testing. B. Responses related to return of VUS in asymptomatic population testing.

exceptions (1.6% [7]). This categorization aided in the aggregation of responses, which were then discussed by the working group and addressed, as appropriate, in the document.

Our survey findings should be considered in light of several limitations. Findings may be biased by participants having self-selected to respond. The majority of respondents (62.1%) were located in the United States; therefore, survey findings predominantly reflect practice and attitudes in the United States. There were limited respondents from patient organizations and given the solicitation of these responses via patient advocacy organizations and not health care settings, findings may not reflect the views of most individuals undergoing genetic testing.

General recommendations

We have outlined below a series of general recommendations for VUS reporting (Figure 3, Box 2) based on the most common germline genetic and genomic testing scenarios and assuming no subclasses of VUS are available. These recommendations refer to test results from any germline genetic or genomic testing platform, including but not limited to chromosomal microarray analysis (CMA), exome sequencing (ES), genome sequencing (GS), multigene panel testing, genotyping, optical genome mapping, and other technologies assessing germline genetic variation. These recommendations do not apply to G-banded karyotype analysis because formal pathogenicity classification is often

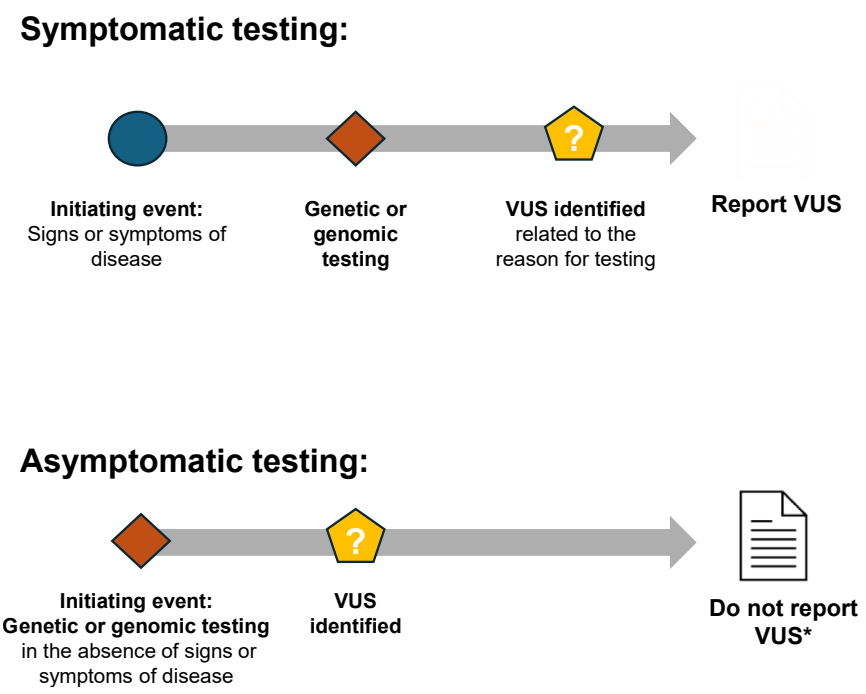

Figure 3 General recommendations for reporting VUS in symptomatic and asymptomatic germline testing. Further detail, contextualization, and examples are provided in the main text. *Exceptions to these general recommendations are described in the text.

not performed, and instead, an abnormal karyotype may include a recommendation to follow up with orthogonal tests that can provide more granular resolution. These general recommendations are then followed by additional considerations related to the use of VUS subclasses and exceptions to the general recommendations. It should be noted that although our survey was distributed globally, and all views were considered, the final recommendations summarized here fall within allowable regulations in the United States today and did not address existing policies or regulations in other countries that may hinder implementation. Furthermore, these recommendations apply to variants related to Mendelian diseases, with a range of penetrance, but do not apply to risk alleles.[40]

Symptomatic testing

VUS are recommended for return in symptomatic germline genetic testing when results are relevant to the phenotype indicated for testing. This relates to all contexts under which individuals are tested, including preimplantation, prenatal (excluding cell-free fetal DNA screening), perinatal, pediatric, adult, and postmortem.[41] The following are additional considerations:

- VUS in genes of uncertain significance (GUS) that are not yet implicated in disease (ClinGen limited strength or below[42]) should be reported if the gene is a strong candidate for the disease (eg, constrained for variation, necessary protein in a pathway implicated in the disease indicated for testing), and there is variant-level evidence consistent with pathogenicity (eg, de novo occurrence, predicted loss of function). More guidance for reporting novel (unpublished) gene-disease candidates in clinical laboratory testing has been published.[43] Laboratories should make clear the distinction between a VUS being reported in a GUS vs a VUS in a gene with an established disease relationship. This can be achieved with clear annotation or by moving these findings to a distinctly labeled section of the report.
- Structural variants (SVs) of uncertain significance that impact genes or regions with noted dosage sensitivity matching the mechanism of disruption (haploinsufficiency or triplosensitivity) associated with the tested individual's phenotype should be reported. This may include SVs with only GUS if 1 or more genes are constrained for variation of similar dosage as the VUS.
- Labs may choose not to report (or move to a supplement or separate section of the report) a VUS when identified in heterozygosity in a gene implicated only in autosomal recessive disease and for which no variant has been identified on the other allele, unless the gene is a very strong match for the tested individual's phenotype.
- In multigene panels encompassing genes for a specific phenotype, all VUS are reportable even if phenotype has not been provided, given the assumption that the test was ordered based on symptoms, unless the test is offered explicitly for asymptomatic testing. However, for multigene panels of large size and breadth of phenotype, many variants may be identified that

Box 2 Key points

- VUS are recommended for return in symptomatic genetic testing when results are related to the phenotype indicated for testing.
- VUS are not recommended for return when identified in testing of asymptomatic individuals in the absence of signs or symptoms of a genetic disease.
- Laboratories are encouraged to include specific follow-up recommendations on genetic testing reports for gathering evidence that is likely to change the VUS classification.
- Laboratories are encouraged to adopt VUS subclasses and should consider methods to bring attention to variants that most likely explain the tested individual's phenotype, including VUS-high, and de-emphasize VUS that are unlikely to be causal.
- Laboratories are encouraged to update reports when variant classifications change.
- It is critical that laboratories share knowledge of variants observed and interpreted during testing, even if not reported, through submission to ClinVar and other methods.
- Collaborative and continuous communication between the clinical laboratory and the provider remains paramount to understanding variation and improving outcomes.

correlate poorly with the clinical features of the tested individual. Efforts should be made by ordering clinicians to provide detailed phenotypes,[44] and laboratories should define whether a reported variant would be expected to explain the phenotype (if provided) based on the level of gene-to-phenotype match.

- In ES/GS, VUS in genes with only limited correlation with the phenotype should either not be reported or be deemphasized, either through noting the limited correlation to the tested individual's phenotype or moved to a supplement or separate section of the report in which variants may be listed with the assumption that they are less likely to be causal to the tested individual's phenotype.

For scenarios in which individuals are asymptomatic but have a family history of a genetic disease or a disease of likely genetic origin, see below (Considerations regarding family history) for guidance.

Asymptomatic testing

VUS are not recommended for return when identified during germline testing of asymptomatic individuals. This includes the following testing scenarios:

- Return of secondary or incidental findings.[26,45]
- Unselected population testing to identify disease risk, such as for cancer or cardiovascular disease.[25]
- Newborn sequencing in the absence of correlated metabolic or clinical findings.
- Pharmacogenomic testing in the absence of clinical evidence and/or family history of an adverse or unexpected response to a medication.
- Prenatal and preconception carrier screening when performed on a single individual.[27,46]
- Prenatal genetic and genomic testing if findings are not correlated to prenatal clinical findings or family history of genetic disease.
  - Note: We recognize that our recommendation to not report VUS in asymptomatic prenatal testing, often performed by CMA testing, may represent a departure from laboratory's current practice but builds on evolving practices and current Canadian recommendations to limit the reporting of VUS in prenatal CMA testing.[47] Traditionally, VUS have been returned from CMA, regardless of indication, based on the observation that copy number variants (CNVs) above a certain size range were more often detected in the clinical population referred for CMA testing compared with controls (see Miller et al,[48] 2010, Cooper et al,[49] 2011; Coe et al,[50] 2014). We now have a few decades of empirical data and further study of human populations, gene properties, gene-disease relationships, and genomic structure to incorporate into CNV classification and reporting decisions that do not need to strictly rely upon CNV size. We also appreciate that the availability of phenotypic information is sometimes limited in the context of CMA testing, which provides additional challenges to contextualize variant interpretation. However, with the availability of new technologies for cytogenomic variant detection that have higher resolution, it is time to reevaluate and align practices to arrive at more standardized and platform-agnostic approaches with regard to VUS reporting, especially given the documented heterogeneity in current practice[51] and guidance that has, to date, been delegated to laboratories to define.[2] Laboratories should align on the provision of a clinical indication for testing as has become standard in ES and GS and is required for many other clinical tests (eg, imaging). Additional guidance for prenatal variant reporting from an ACMG working group is forthcoming and should better delineate and standardize reporting practices with the goal of unifying across labs and ensuring appropriate reporting of prenatal VUS.

Considerations regarding family history

- For genetic testing where the indication is reviewed during interpretation, return of VUS should be considered if it affects 1 or more genes associated with a disease for which the individual has a family history that is highly suspicious for a genetic etiology or the variant relates to known genetic findings.

- Although VUS are generally returned during multigene panel testing with an assumption of symptoms in the individual tested, for certain panel-based tests that are commonly used in both asymptomatic and symptomatic testing (eg, cancer risk screening, living organ donation), labs may consider offering testing in 2 versions: 1 with VUS return, and 1 without, and guide clinicians ordering testing for individuals with family histories that suggest a high prior probability of a genetic etiology, to order the test with VUS returned.

Considerations for applying VUS subclasses in reporting

In the upcoming standards for variant classification for sequence variants (SVCv4.0), specific guidance will be provided on how to subdivide VUS based on a point-based system, as well as providing standardized terms for these subclasses (eg, VUS-low, VUS-mid, VUS-high). The SVCv4.0 guidance will specify the point ranges for each VUS subclass such that all VUS will be consistently subclassified by evidence level. For laboratories that have not yet implemented subclasses, it may be appropriate to wait until the SVCv4.0 standards are published. Updated CNV guidance will also follow. However, many laboratories already use VUS subclasses, and the following guidance is applicable.[28,38]

Application of VUS subclasses will allow tracking of VUS subclass outcomes and to inform future policy development for genetic testing reports. In particular, multigene panel testing reports currently have high rates of VUS, and we recommend that laboratories explore approaches to reduce the negative impact and optimize positive implications of VUS return. We suggest the following points be considered.

- We strongly recommend that laboratories include VUS subclass terms on reports, along with access to explanations of these terms. This allows clinicians and individuals undergoing testing to know which variants, as evidence emerges, are more likely to move toward pathogenic vs those more likely to move toward benign. Stratifying VUS may also assist with VUS resolution by prioritizing variants for which to generate additional evidence (eg, pursuing family studies). Given health care resource constraints, prioritizing follow-up for VUS-high, which are more likely to be reclassified as LP, may be warranted.
- Laboratories should consider methods to bring attention to variants that most likely explain the indicated phenotype or family history and reduce attention on those variants that are unlikely to be causal. The following are distinct mechanisms that may be explored to achieve this goal:
  - Consider partitioning VUS, particularly VUS-low variants, into separate sections or supplements of the report where they can be deemphasized if needed. For ES/GS, a list of variants reviewed but less likely causal could be included as a supplement. In these cases, the full Human Genome Variation Society variant nomenclature, gene symbol, associated disease, and inheritance, as well as parent of origin, if known, should be included with each variant.
  - Consider not reporting VUS-low variants. This approach is best considered when testing has a low prior probability of identifying a causal variant and follow-up approaches are less likely to yield more evidence (eg, most germline cancer testing).

In deploying these approaches, we encourage laboratories, clinics, and research programs to gather and publish feedback and data on the experience of using different approaches to VUS return to best inform future practices that could be further standardized. Current experience in VUS subclass reclassification is based on nonstandardized laboratory practices and therefore, once laboratories implement SVCv4.0 standards, we encourage laboratories to track the likelihood and direction that variants in each subclass get reclassified to further inform VUS reporting practices and policies.

Exceptions

The recommendations provided above attempt to balance benefit and harm for the most common testing scenarios, a wide range of clinical expertise among ordering clinicians, and generally limited health care resources to support the ordering and return of genetic test results. However, the balance of benefit and harm can be altered through the addition of genetics expertise, more genetic counseling support, additional resources to support test ordering and return of results and test preparation through education. In these exceptional settings, we recognize that return of a wider range of results could be handled appropriately.

The distinct perspectives of our patient and patient advocacy group respondents, who generally would prefer the return of more uncertain results compared with laboratories and clinicians, indicate that there is demand for detailed genetic information regardless of certainty. Although not recommended for general practice, we note that rare exceptions could include offering tested individuals the choice of receiving VUS in asymptomatic testing or opting out of receiving VUS in symptomatic testing. These allowances could be further delineated by VUS subclass (eg, opting out of VUS-mid and VUS-low only). However, we recognize that these allowances would require extensive pretest counseling support, as well as customized test options by laboratories that are unlikely to be practical for most testing scenarios. Of note, the patient groups surveyed were highly engaged through advocacy organizations and therefore may not be representative of the general population receiving genetic test results.

Although generally not recommended for routine testing, the following are scenarios in which justifiable exceptions could be made for returning VUS in asymptomatic testing, provided that there is pretest education, explicit consent, and genetic counseling support for the individual being tested.

- In preconception and prenatal carrier screening, VUS-high can be considered for return when identified in the same gene as a P/LP variant found in a reproductive partner, with consent from the individual undergoing testing.[27,46] This also applies to carrier testing for pregnancies using egg or sperm donors. We strongly encourage clinicians to order simultaneous carrier screening on both reproductive partners. If initial testing was not performed through partner-based analysis, requests to the testing laboratory to reexamine results when the lab is supplied with the current reproductive partner's results should be available as a service. At this time, we do not recommend that monoallelic or biallelic VUS be returned if identified in the same gene in both reproductive partners, and there is no P/LP variant in either partner; further studies on the outcomes of reporting VUS in carrier screening are needed before more widespread return of VUS can be recommended.
- In population testing for highly actionable conditions, VUS-high could be considered for return.
- In pharmacogenomic testing for severe drug-induced toxicity, VUS-high could be considered for return.
- In prenatal testing, where phenotypes are less clear and decision-making opportunities exist, VUS-high could be considered for return.
- In newborn screening, VUS-high may be returned if found in trans with a P/LP variant in a gene related to a recessive disorder, if confirmatory clinical or biochemical testing is available for the disorder.

VUS follow-up language and considerations

Laboratories are encouraged to include specific follow-up recommendations on reports harboring VUS to gather evidence likely to change the variant classification. For example, laboratories might note when parental testing is recommended to determine de novo occurrence if it will move the variant from VUS to pathogenic. Furthermore, laboratories are encouraged to request that any findings or results obtained by the clinician after reporting, that may inform variant reclassification, be relayed back to the lab.

We note that VUS follow-up is labor intensive for laboratories and clinicians and may not be possible in many circumstances. However, the use of VUS subclasses will likely reduce the quantity of variants where VUS follow-up is pursued. Although this may reduce the fraction of VUS-low variants that get moved to B/LB, widespread data sharing and improved diversity of population databases are likely to be the most cost-effective approach to tackling VUS-low.

Points to consider in updating reports after variant reclassifications

Laboratories are encouraged to update reports when variant classifications change. Some laboratories have robust systems to deliver report updates, including variant reclassifications, to ordering clinicians; other laboratories may take a priority-based approach to determine which reports are updated in the absence of a specific clinician request. For example, P/LP or B/LB variants that move to VUS or further (eg, P/LP to B/LB or vice versa) are the highest priority for updated reporting given the low likelihood and lack of anticipation that these changes occur. Second priority are variants that move from VUS to either B/LB or P/LP. Lowest priority are variants moving within a category (LP to P or LB to B). As laboratories move to the use of VUS subclasses, more changes must be considered. For example, changes between VUS-low and VUS-high are likely to be a higher priority for report updating than changes between P and LP or B and LB. Laboratories are encouraged to explore clinician preferences for updating reports. The increasing integration of laboratory and electronic health record systems as well as implementation of automated laboratory solutions will ease the burden of sharing updated knowledge.[52]

Implementation considerations

We recognize that there may be challenges related to the implementation of some of these recommendations. Furthermore, VUS subclass use will be new for most laboratories and clinicians, and there is limited experience with reporting subclasses, beyond a subset of laboratories.[38] As such, we suggest several approaches that laboratories may explore to minimize harms and maximize benefits of reporting VUS without defining a single best approach. We recognize that this will likely lead to practice variation across laboratories. It will be important for laboratories to clearly communicate their policies for the use of VUS subclasses. In particular, and whenever feasible, it is recommended that reporting practices (including policies on returning of VUS), as well as test limitations, be discussed with providers before making the clinical test available to order or whenever testing updates are undertaken. It should also be noted that certain regulatory bodies (eg, CAP) require providers to be notified of any significant changes to test reporting parameters. We also encourage laboratories and clinician communities to publish on their approaches and experiences with VUS subclasses, to inform future standardized guidance.

Some of the scenarios above are predicated on clinicians providing a clear indication for testing and phenotype information that would allow correlations between variant(s) and the phenotype or family history of the tested individual. When laboratories do not receive detailed clinical information, they may need to take a more permissive approach to

reporting VUS in the context of symptomatic testing, to avoid missed reporting of potentially relevant variants. With detailed clinical information, laboratories may be better able to deemphasize or omit VUS/VUS-low that are unrelated to the phenotype or family history of the tested individual. We encourage ordering clinicians to provide detailed data on the phenotype and family history of the tested individual, including features that may not seem related to the indication for testing.[44] Similarly, laboratories are encouraged to provide mechanisms to collect additional clinical information that could inform interpretation and reporting.[44] Increased integration with electronic medical records may facilitate communication between laboratories and clinics.[53]

Variant reevaluation and recontact pose practical challenges given limited staff time and resources, and the ACMG has published separate guidance on these topics.[54,55] Establishing reimbursement mechanisms for these services could help to promote consistency.[54] Automation may promote the feasibility of variant reevaluation,[56,57] and the use of VUS subclasses will likely have utility for prioritizing variants for reevaluation because VUS-high are most likely to be reclassified to P/LP.[38] Use of patient registries or online portals could promote the feasibility of recontacting tested individuals or their clinicians with variant classification updates.[58]

Equity considerations

Many studies have demonstrated higher rates of VUS among genetic ancestry groups that are underrepresented in genomic research,[13,59-64] as well as lower rates of positive diagnostic findings[60,62,63,65] because there is less evidence available on causal variants in underrepresented populations. The use of VUS subclasses may be beneficial in underrepresented populations, to garner attention for VUS-high variants that could be causal but lack sufficient evidence to reach a classification of P/LP, and to likewise deemphasize a larger quantity of VUS-low variants that are unlikely to be causal but are not able to reach a classification of B/LB due to limited data from underrepresented genetic ancestry groups. We encourage data sharing, improved access to genetic testing, and more comprehensive population datasets to enable all individuals to benefit equally from genetic testing.[66]

Consideration for the return of research results

Although these points to consider are geared toward clinical laboratories, in many cases the principles are relevant to return of research results as well. However, important differences may occur in research settings. Research and clinical care have distinct goals and guiding principles, and the results that are returned to research participants may vary from clinical practice.[67] A given study may be more or less equipped to follow-up on variants and update reports or other communications over time.[68] If an Institutional Review Board protocol for the study is closed, there may be no path for a researcher to continue to engage a study participant.[68] In contrast, research studies may be well poised and funded to perform follow-up investigations, in which case VUS may be immediately studied to build evidence. Given the wider range of time to return results in research studies, investigators may wish to wait to generate evidence before returning a result, if the time to generate that evidence is not exceedingly long. Also, research studies may wish to partner with clinical laboratories such that long term management of results can be done by the clinical laboratory.

Data sharing

It is critical that laboratories share knowledge of variants observed and interpreted during testing, even if not reported, including submission to ClinVar, which now supports VUS subclasses, and inclusion of the evidence for variant classification in each submission.[69,70] Explicit consent is not required to include phenotypes that have been identified during testing and the evidence from such testing (eg, de novo occurrence, segregation).[70] Patient registries that enable consent to data sharing can help to enhance the detail and quantity of evidence that can be shared.[58] This data sharing will ensure that all variants, including VUS, will benefit from emerging evidence through observations and experimental studies.

Summary

The overarching goal of this points-to-consider document is to help balance potential benefits of reporting VUS (eg, enabling clinician follow-up to obtain further data that may resolve the VUS) with potential harms (eg, patient distress, inappropriate medical care, excessive health care resources expended). The prior probability of a variant being pathogenic in a given testing scenario was a key consideration that strongly guided the workgroup's recommendations for VUS reporting. The ability to use VUS subclasses is anticipated to provide critical distinction to clinicians seeking guidance on the importance of following up on a VUS and informing clinical care recommendations. Once subclass definitions and recommendations are more widely available, laboratories will be in a better position to adopt these subclasses and begin exploring the best mechanisms to use the subclasses to aid in the emphasis and deemphasis of VUS identified during genetic testing. Furthermore, as in all clinical testing, a collaborative and continuous communication between the clinical laboratory and the providers remains paramount in understanding variation and improving outcomes.

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Conflict of Interest

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Additional Information

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Affiliations

[1]Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA; [2]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Medical Genetics and Genomics Division, Department of Pediatrics, Boston Children's Hospital, Boston, MA; [5]Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY; [6]The Steve and Cindy Rasmussen Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, OH; [7]Departments of Pathology and Pediatrics, The Ohio State University, Columbus, OH; [8]Robert J. Tomsich Department of Pathology and Laboratory Medicine, Diagnostics Institute, Cleveland Clinic, Cleveland, OH; [9]Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT; [10]ARUP Laboratories, Salt Lake City, UT; [11]Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, PA; [12]Ambry Genetics, Aliso Viejo, CA; [13]Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA; [14]Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA; [15]Illumina, San Diego, CA; [16]Stanford Medicine Clinical Genomics Program, Stanford University School of Medicine, Stanford, CA; [17]Center for Cancer Genetics and Prevention, Dana Farber Cancer Institute, Boston, MA; [18]Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA; [19]Revvity Omics, Pittsburgh, PA; [20]American College of Medical Genetics and Genomics, Bethesda, MD

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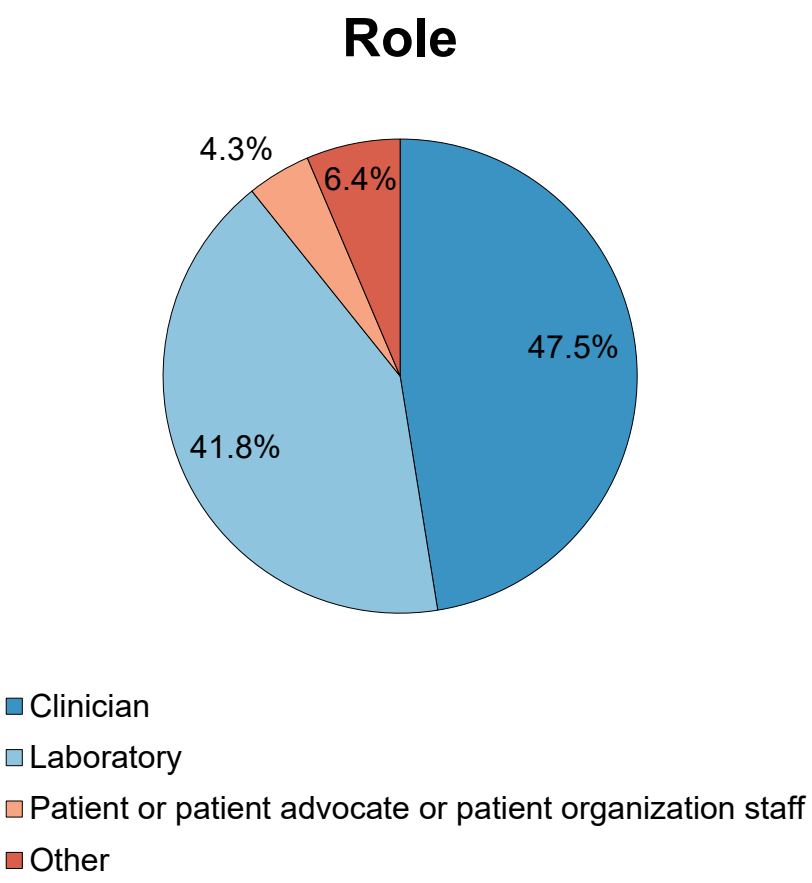
Supplemental Material

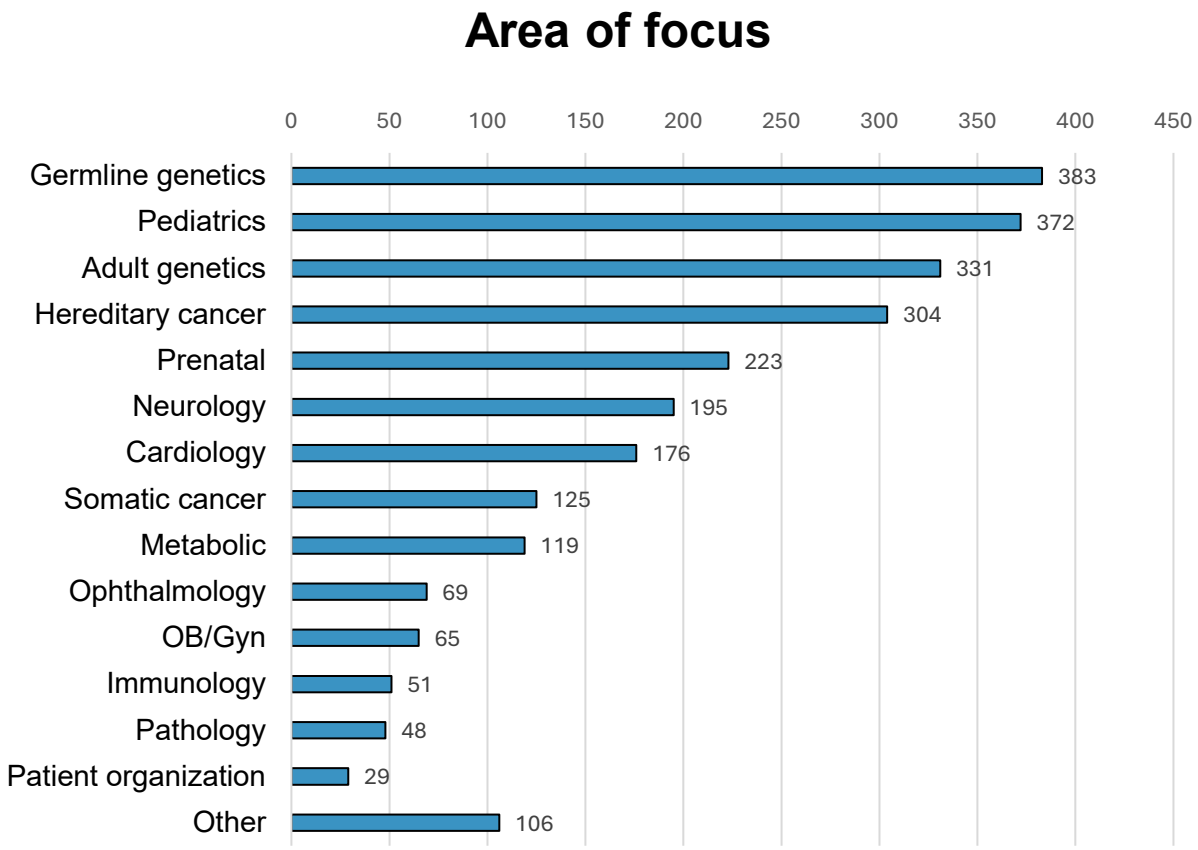
Points to consider for the reporting of variants of uncertain significance in germline genetic and genomic testing: A statement of the American College of Medical Genetics and Genomics (ACMG)

Chloe Mighton, MSc, PhD, Aya Abu-El-Haija, MD, MPH, Vimla Aggarwal, MBBS, Yassmine MN Akkari, PhD, Caroline Astbury, PhD, D. Hunter Best, PhD, Laura K. Conlin, PhD, Steven M. Harrison, PhD, Nan Jiang, PhD, Paul Kruszka, MD, Dianalee McKnight, PhD, Tiffany T. Nguyen Dolphyn, MS, CGC, Farid Barquet Ramos, MS, MPH, Christie P. Thomas, MD, Lora J. H. Bean, PhD, Heidi L. Rehm, PhD; on behalf of the Laboratory Quality Assurance Committee

VUS Reporting Survey Results

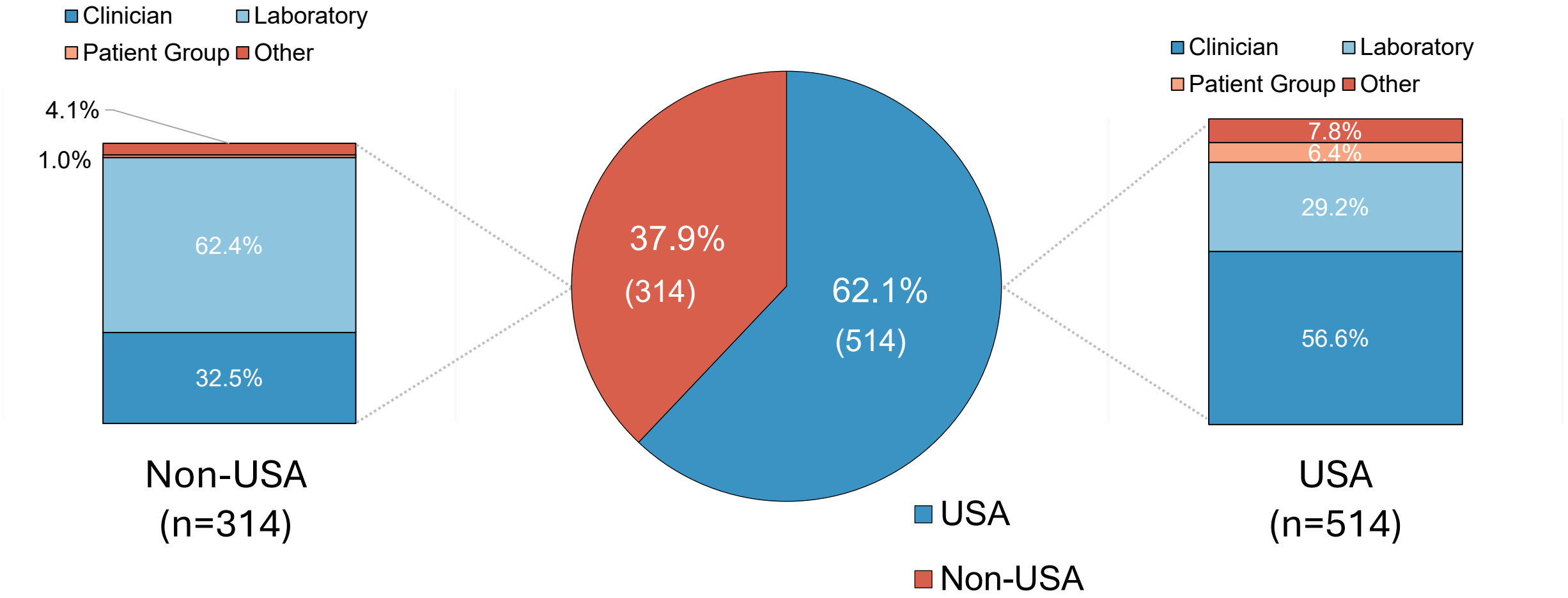
Sample characteristics (n=828 respondents)





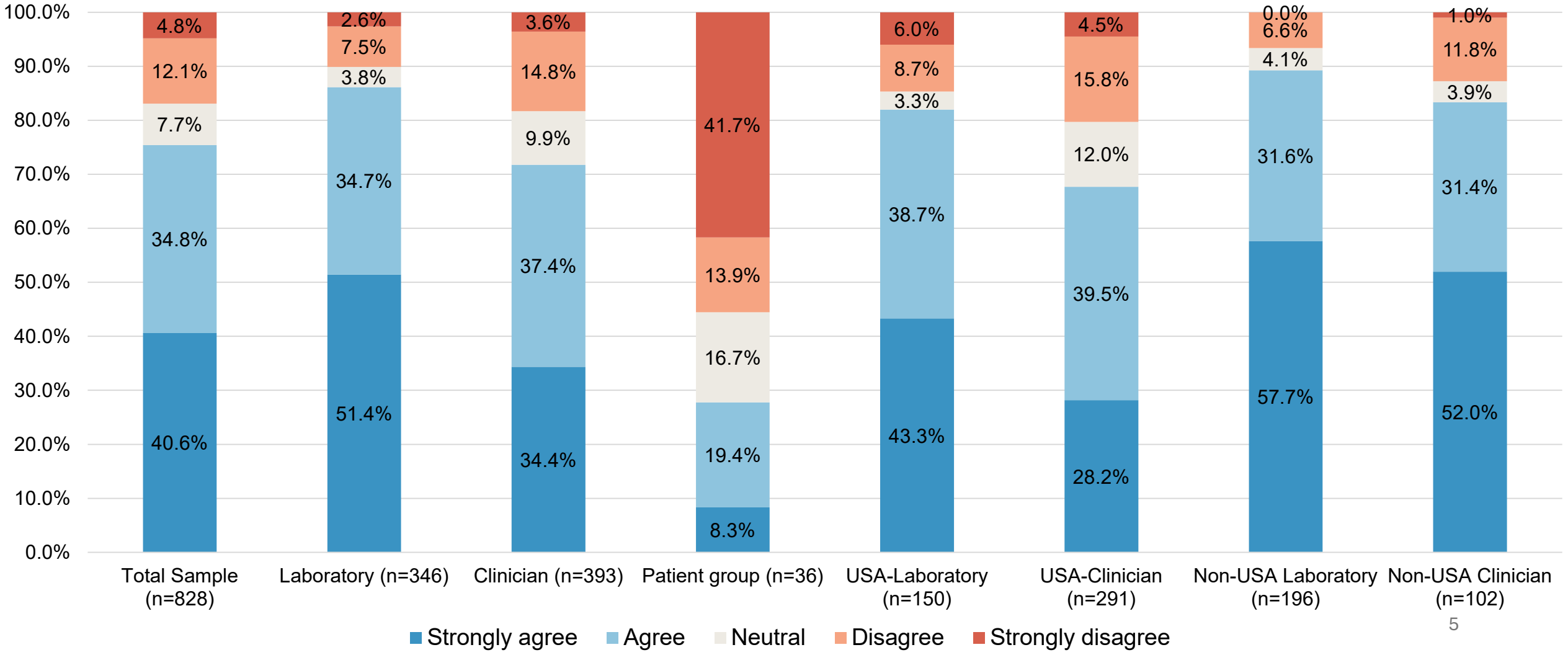
Clinician=Medical geneticist, non-medical geneticist physician, clinical genetic counselor
Laboratory=Laboratory director or analyst, laboratory genetic counselor
“Area of focus” lists the categories with >20 responses, all others grouped into “Other”; respondents could select multiple responses

Sample characteristics (n=828 respondents)

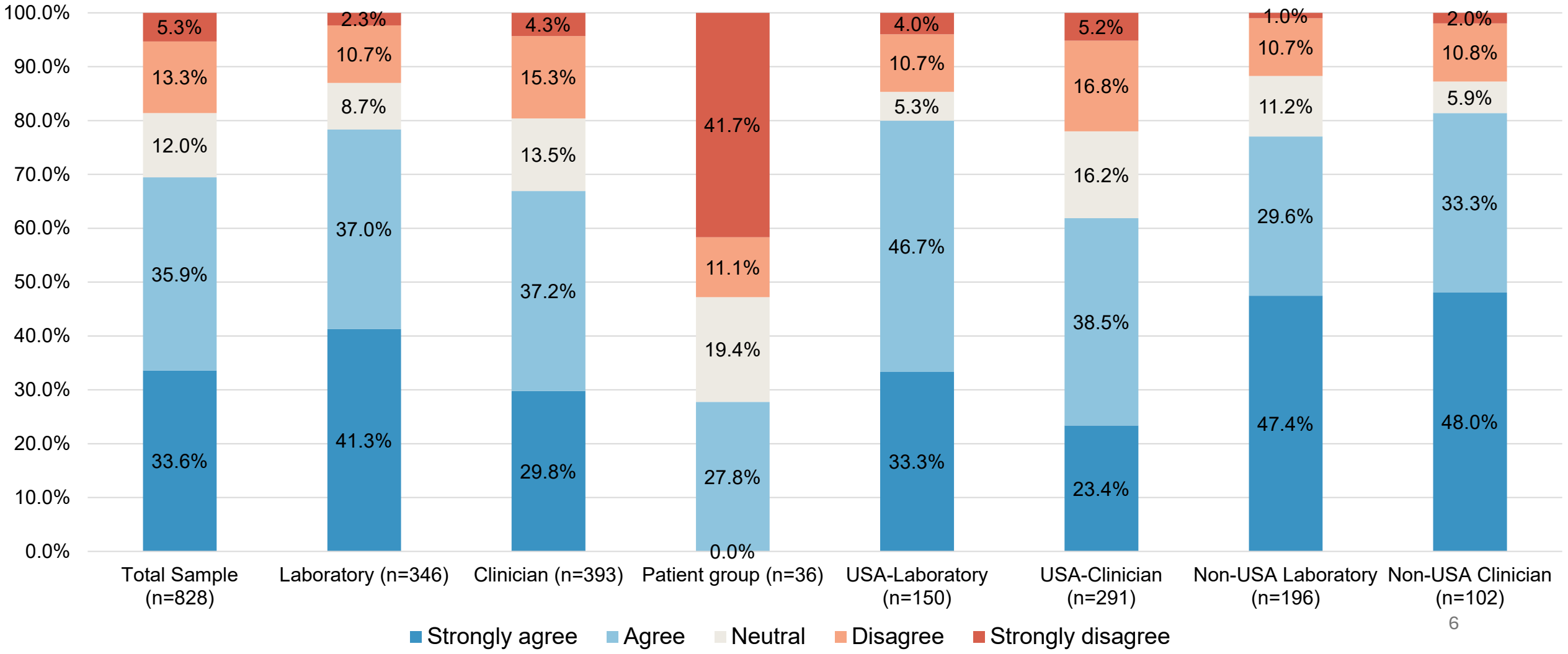


Non-USA=Respondents located in 42 countries

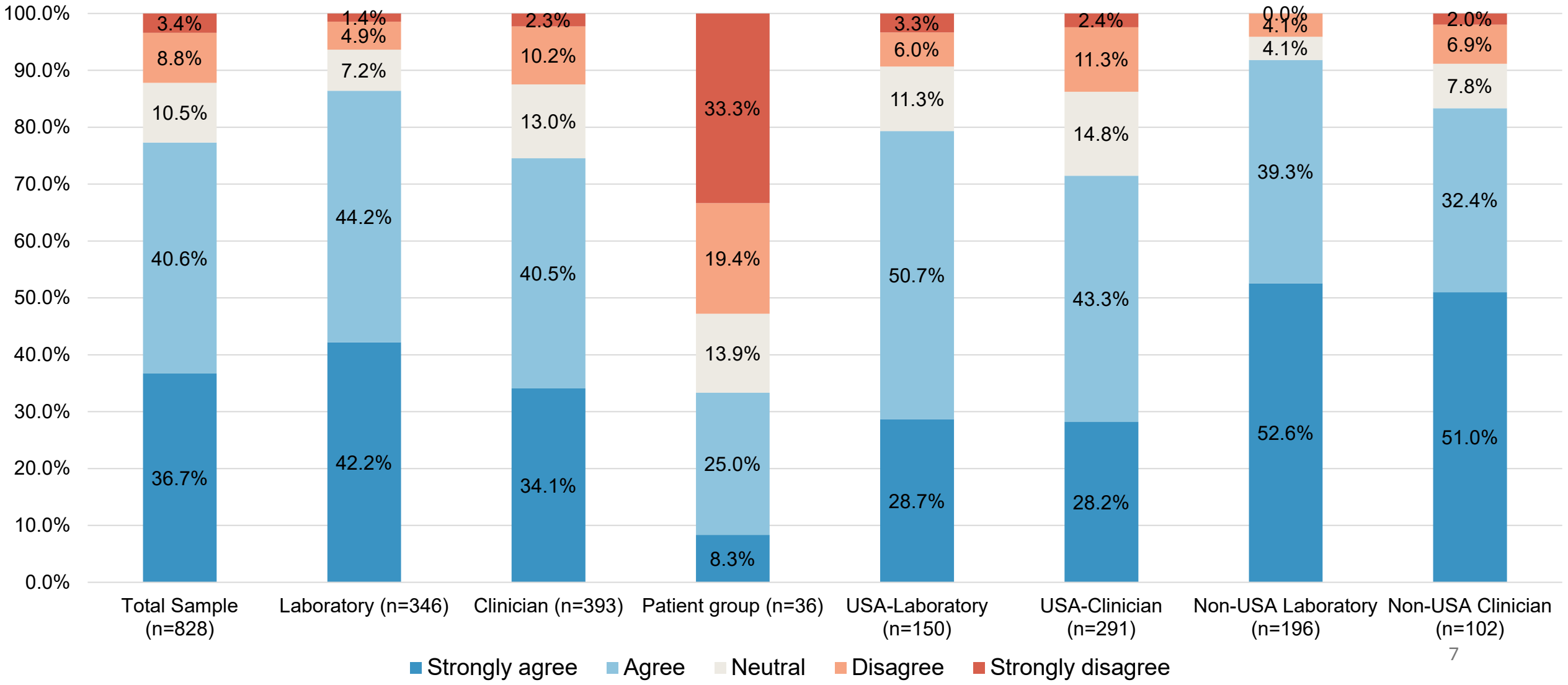
When performing symptomatic exome and genome sequencing (ES/GS) testing, laboratories should NOT return VUS in genes related to secondary or incidental findings (e.g. there are no symptoms or family history of genetic disease related to the finding).



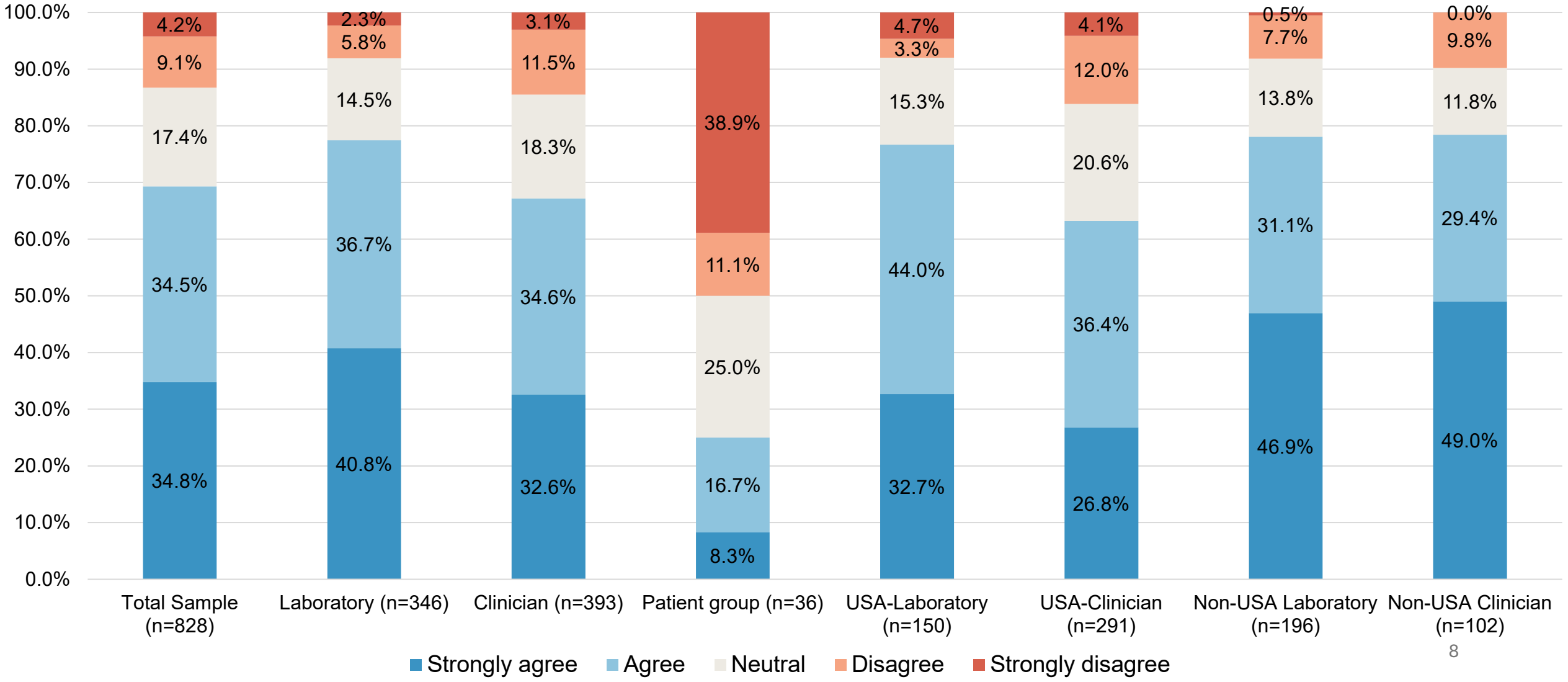
Laboratories should NOT return VUS in population testing performed to identify disease risk such as for cancer or cardiovascular disease.



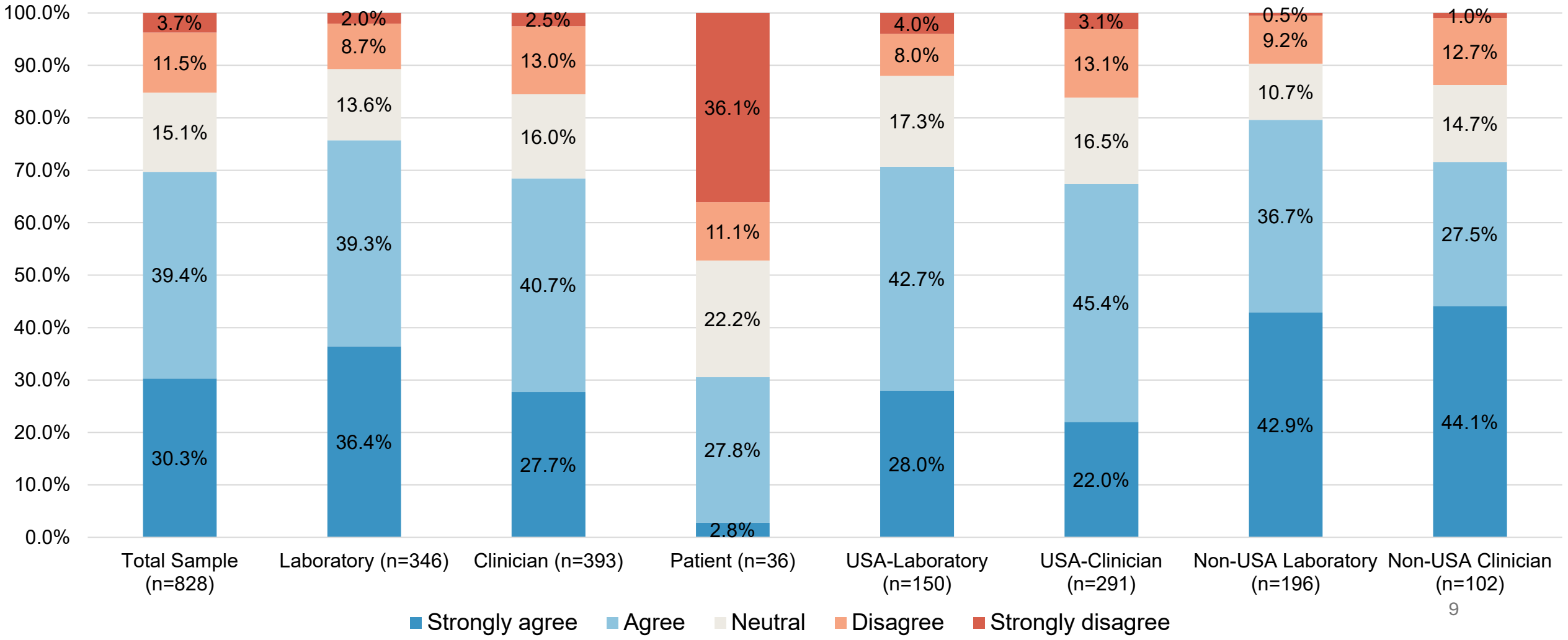
Laboratories should NOT return VUS in newborn screening tests in the absence of correlated metabolic or clinical findings.



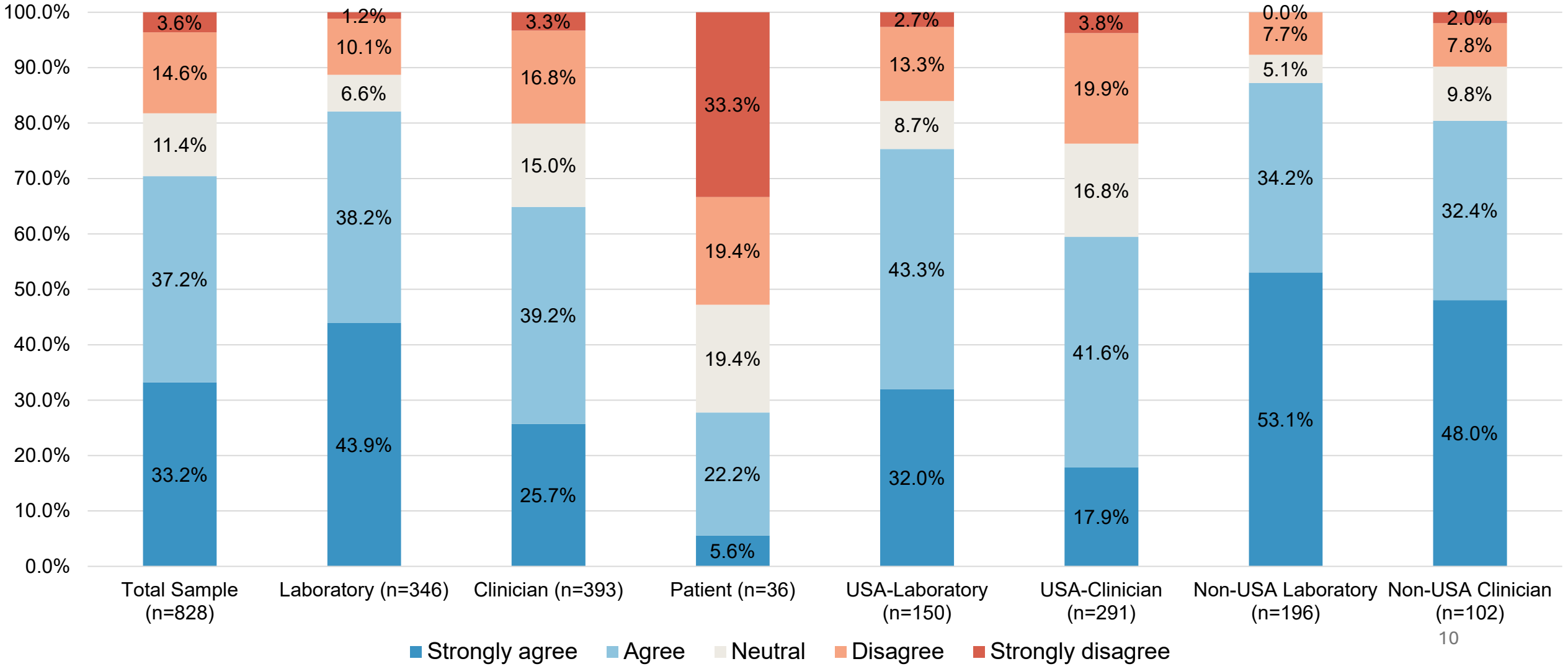
Laboratories should NOT return VUS in pharmacogenomic testing in the absence of clinical evidence of an adverse or unexpected response to a medication.



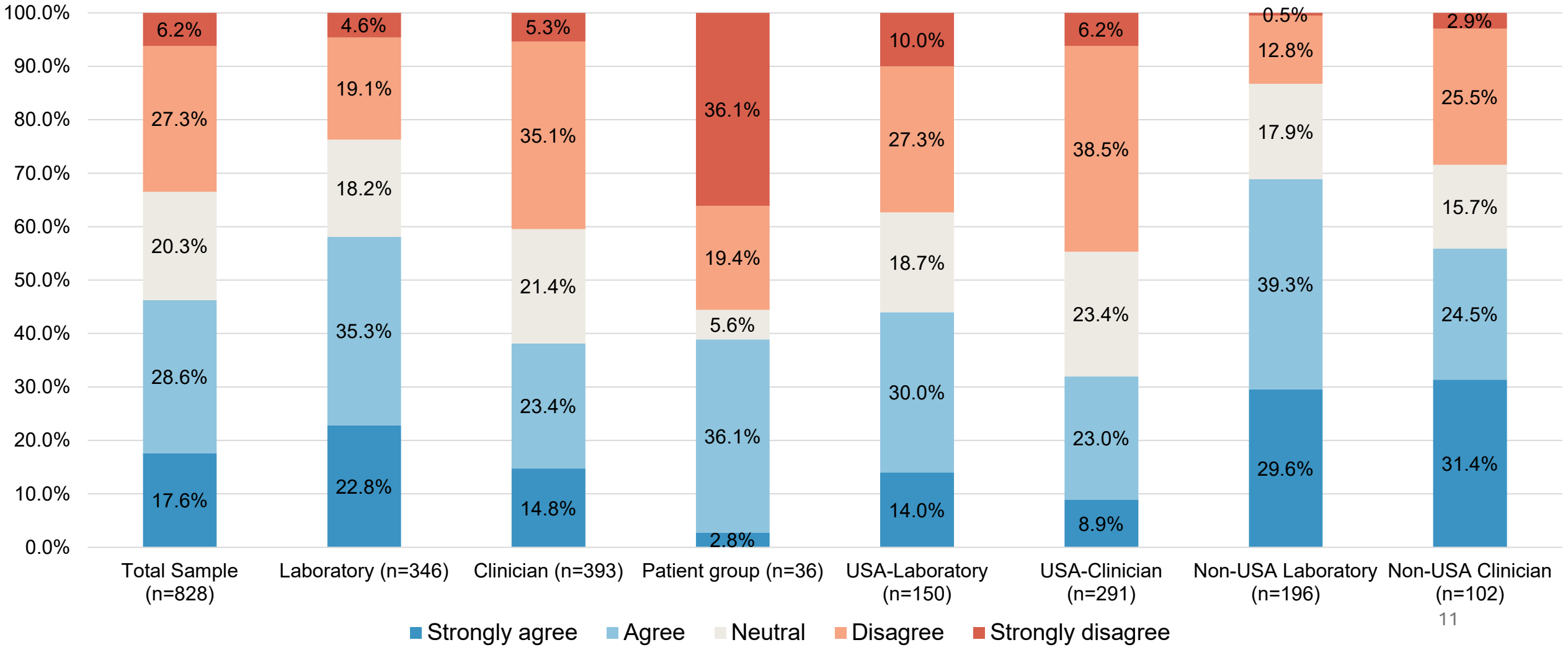
Laboratories should NOT return VUS in carrier screening when performed on a single individual.



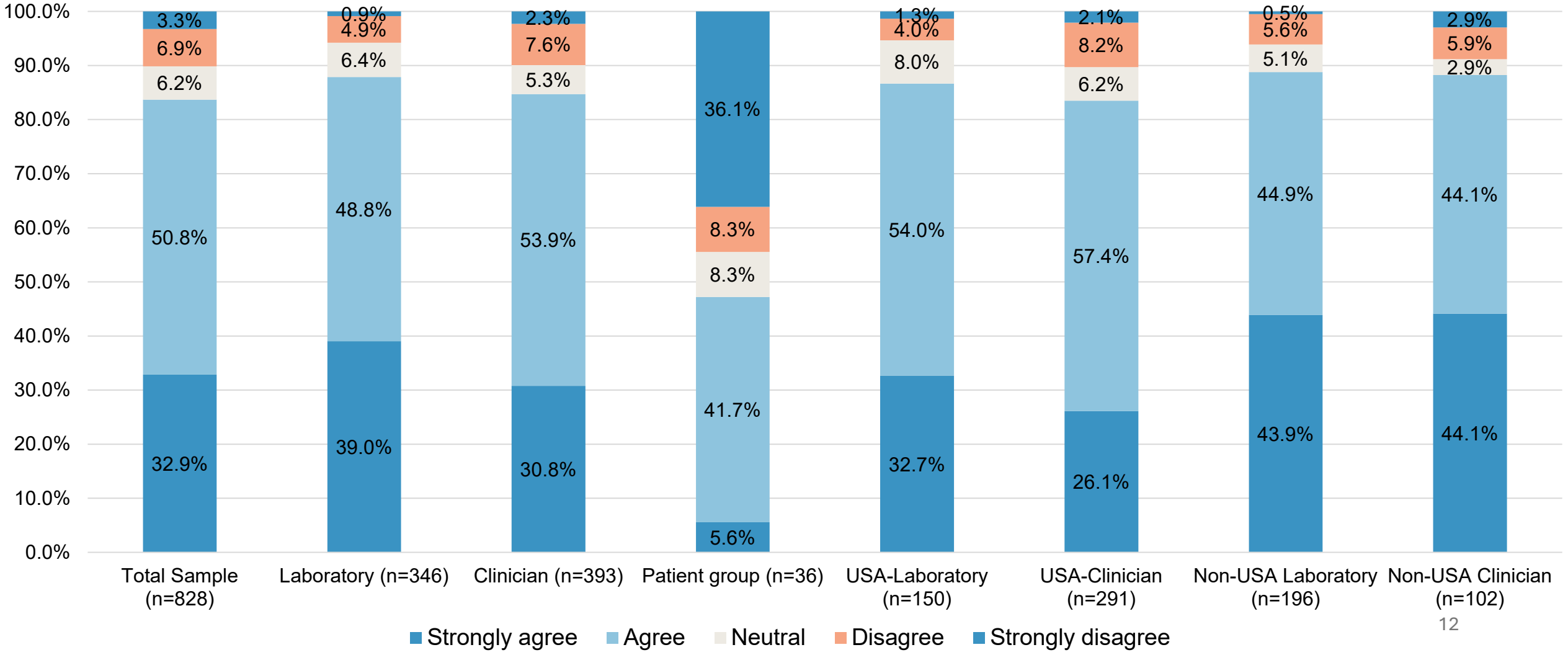
Laboratories should NOT return VUS in prenatal genomic testing (e.g. cytogenomic microarray, exome/genome sequencing) if findings are not related to ultrasound findings or family history of known genetic disease.



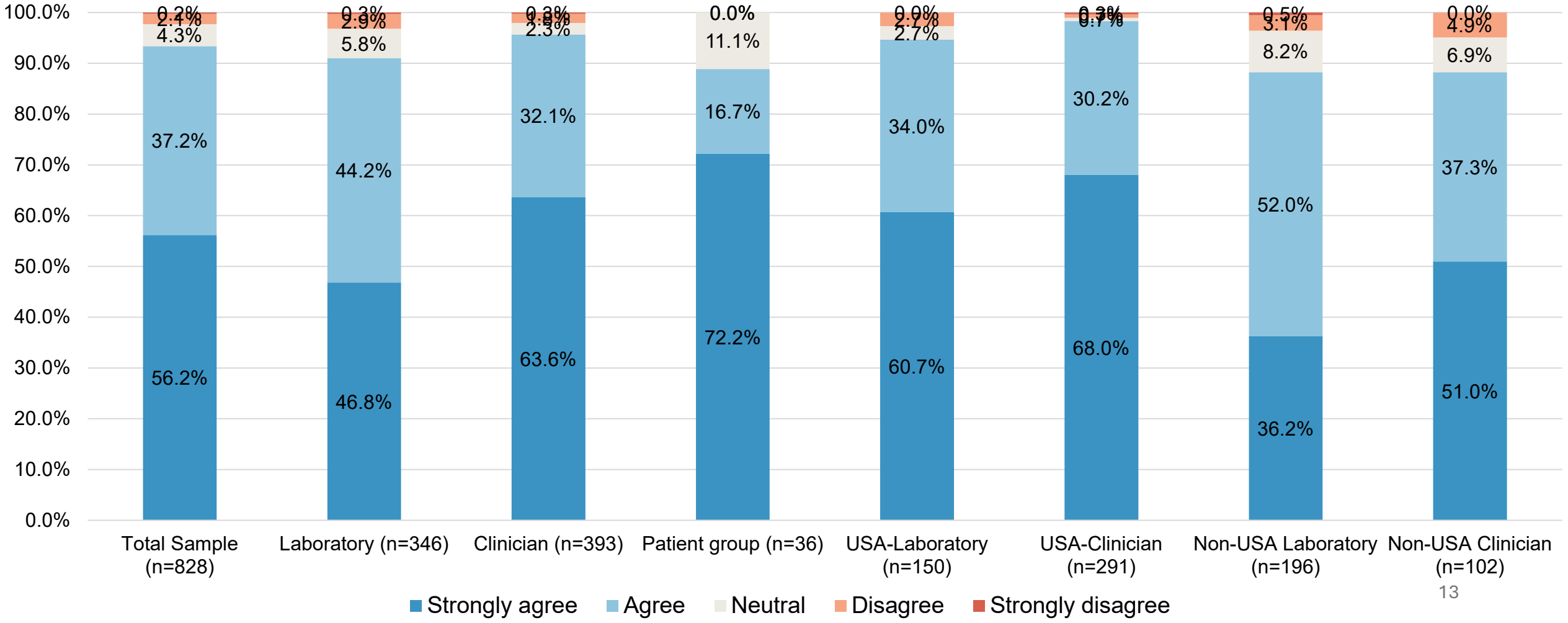
Laboratories should NOT return VUS in postnatal germline cytogenomic microarray testing if findings are not related to symptoms or family history of known genetic disease.



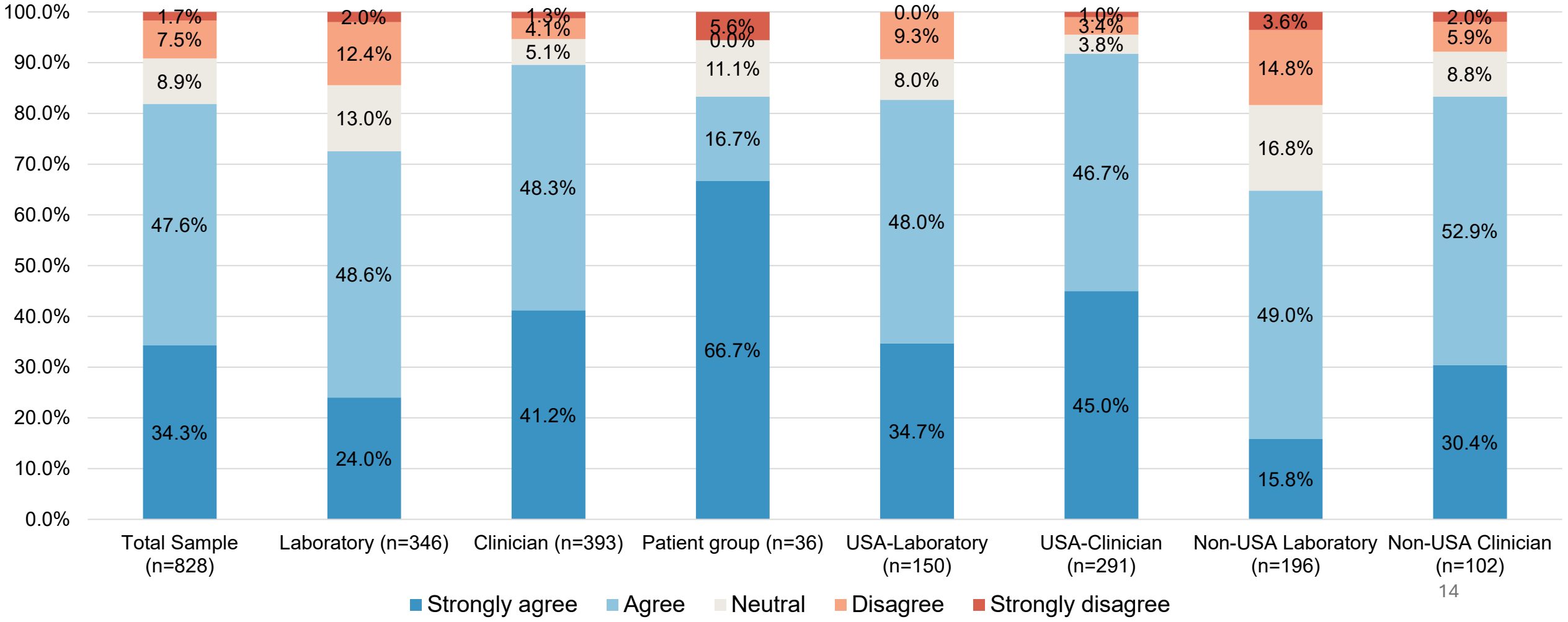
During genome or exome sequencing tests for symptomatic patients, labs may exclude from reporting or de-emphasize (e.g. move to a separate section or supplement) VUS when identified in heterozygosity in a gene implicated only in autosomal recessive disease and for which no variant has been identified on the other allele, unless the gene is a very strong match for the patient's phenotype.



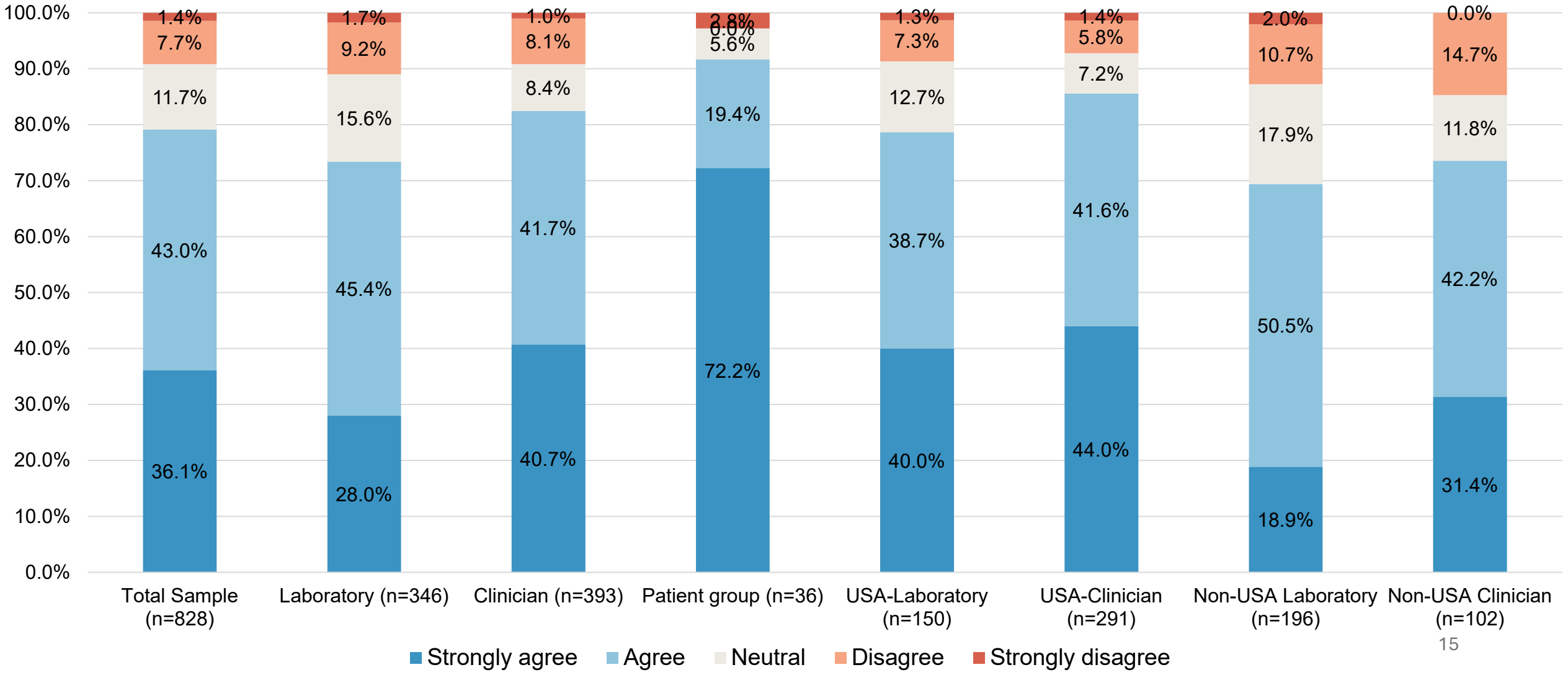
VUS are recommended for return in most symptomatic genetic testing when results are specifically related to the phenotype indicated for testing, including clinical symptoms and/or a family history of genetic disease.



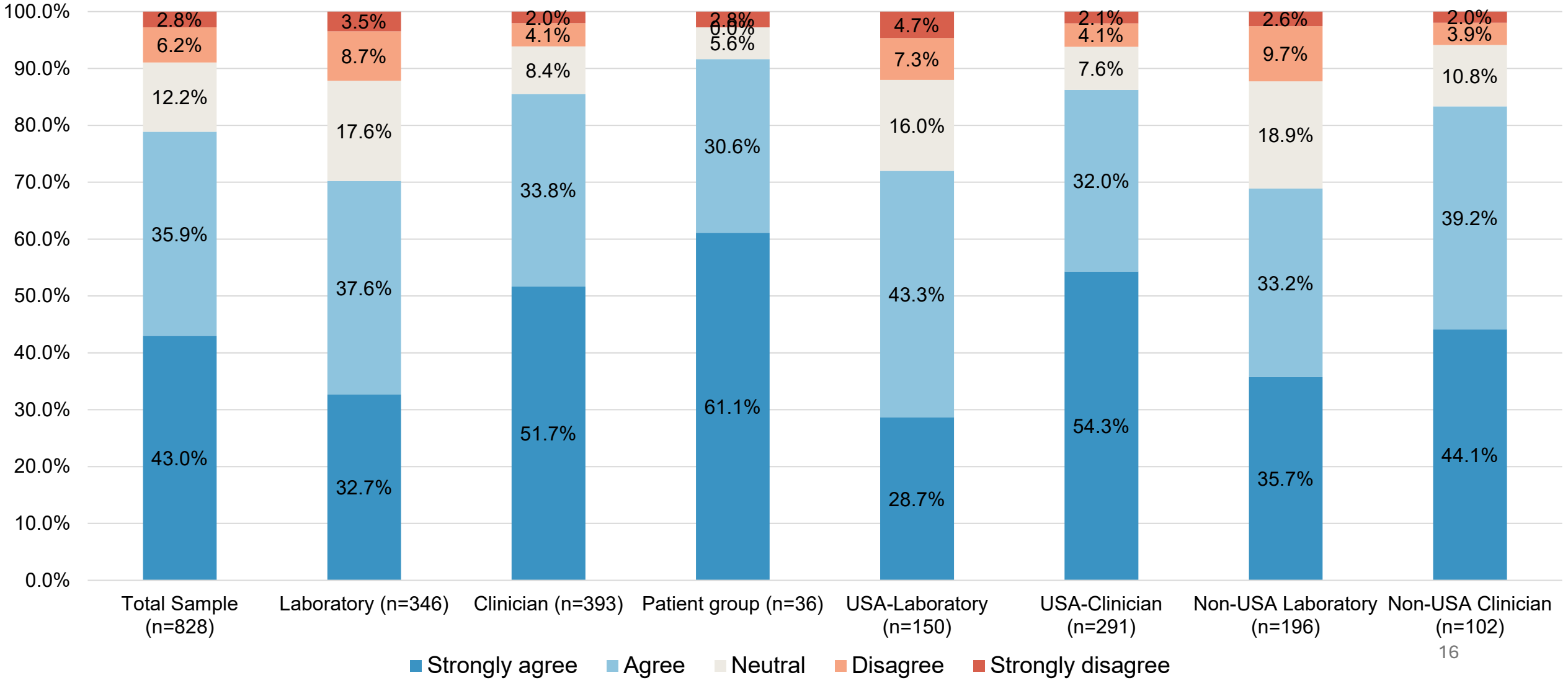
During genome or exome sequencing tests, VUS are recommended for return when found in a single gene that is not yet implicated in disease (ClinGen evidence level of Limited or below) if the gene is a strong candidate for the disease (e.g., constrained for variation, necessary protein in a pathway implicated in the patient's disease) and there is evidence consistent with variant pathogenicity (e.g., de novo occurrence, predicted loss-of-function) and the gene level of evidence is explained in the report.



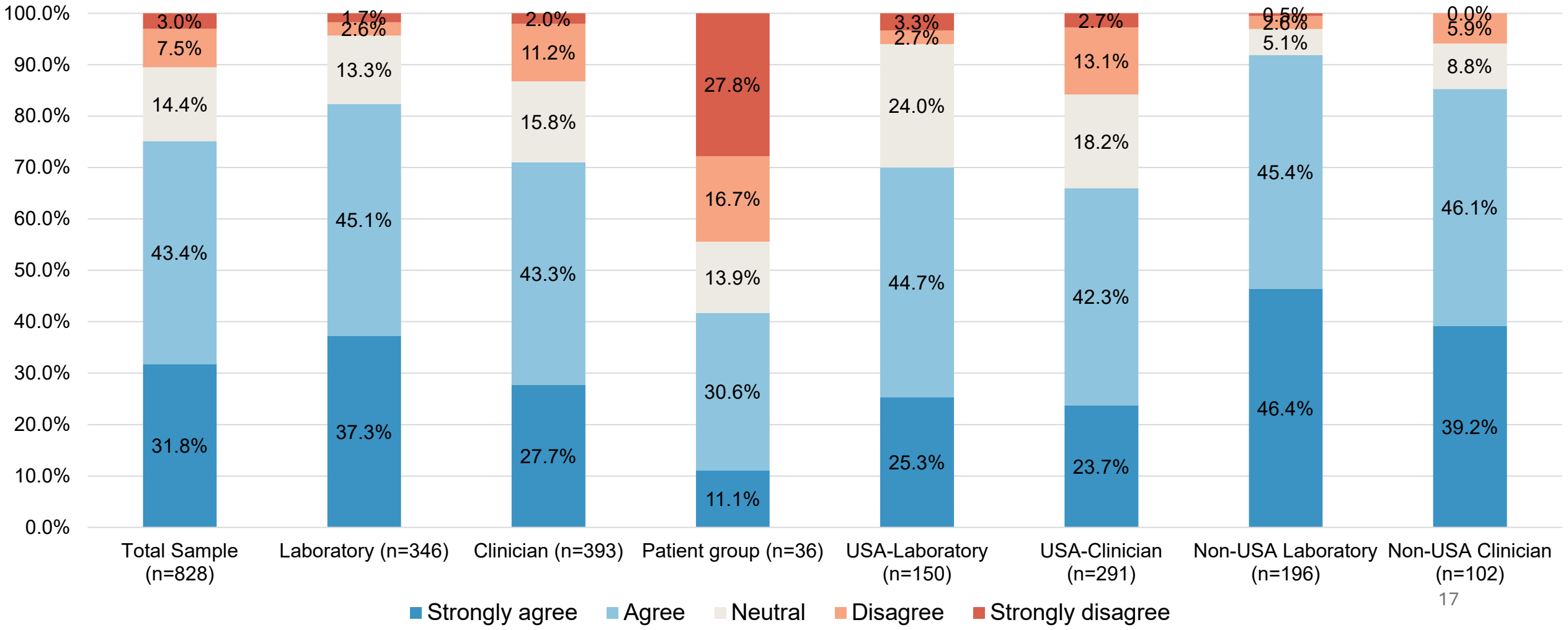
In carrier screening, VUS are recommended for return when identified in the same gene implicated in autosomal recessive disease as a P/LP variant found in a reproductive partner.



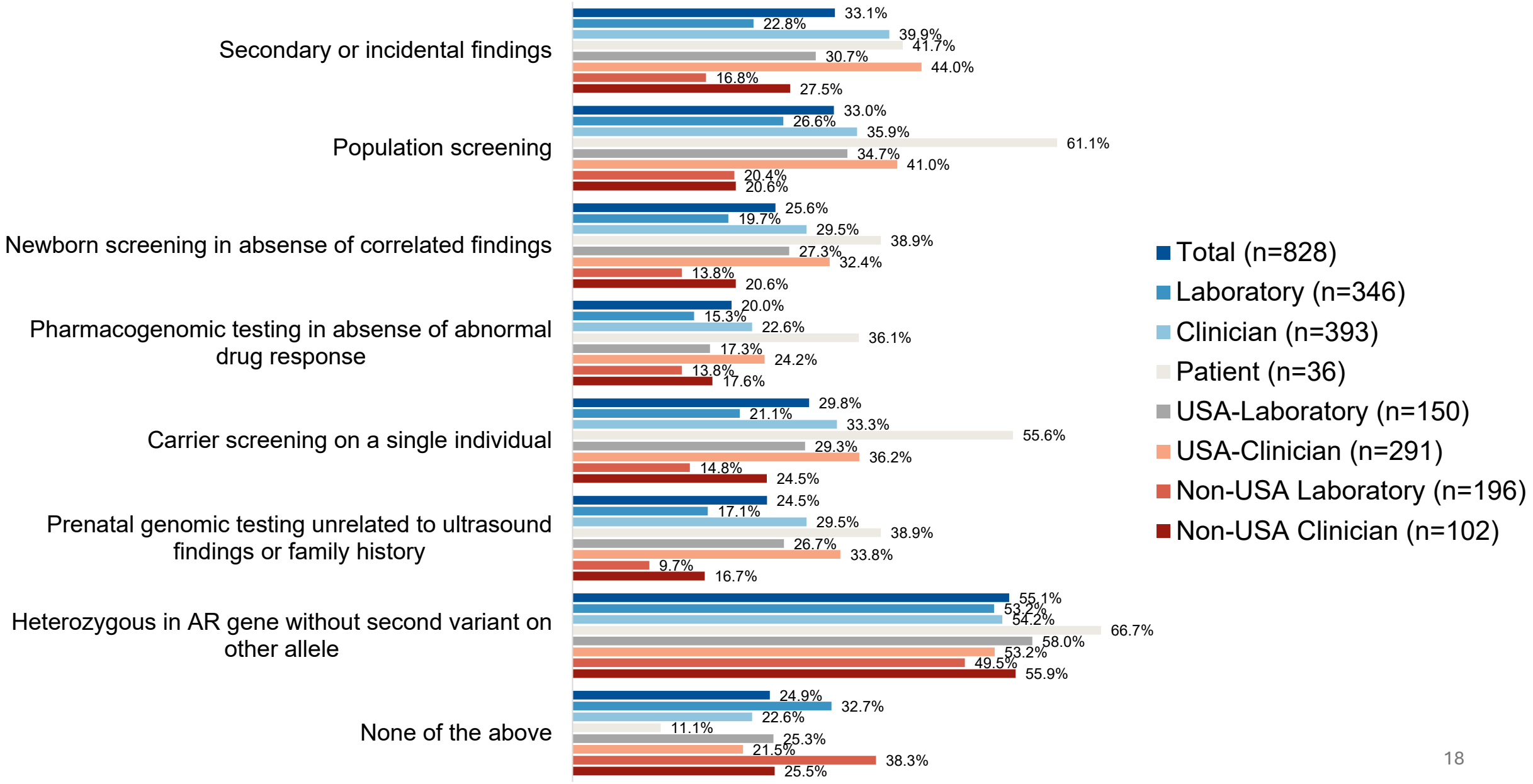
Laboratories should include VUS subclass terms on each VUS in a report, along with access to explanations of these terms.



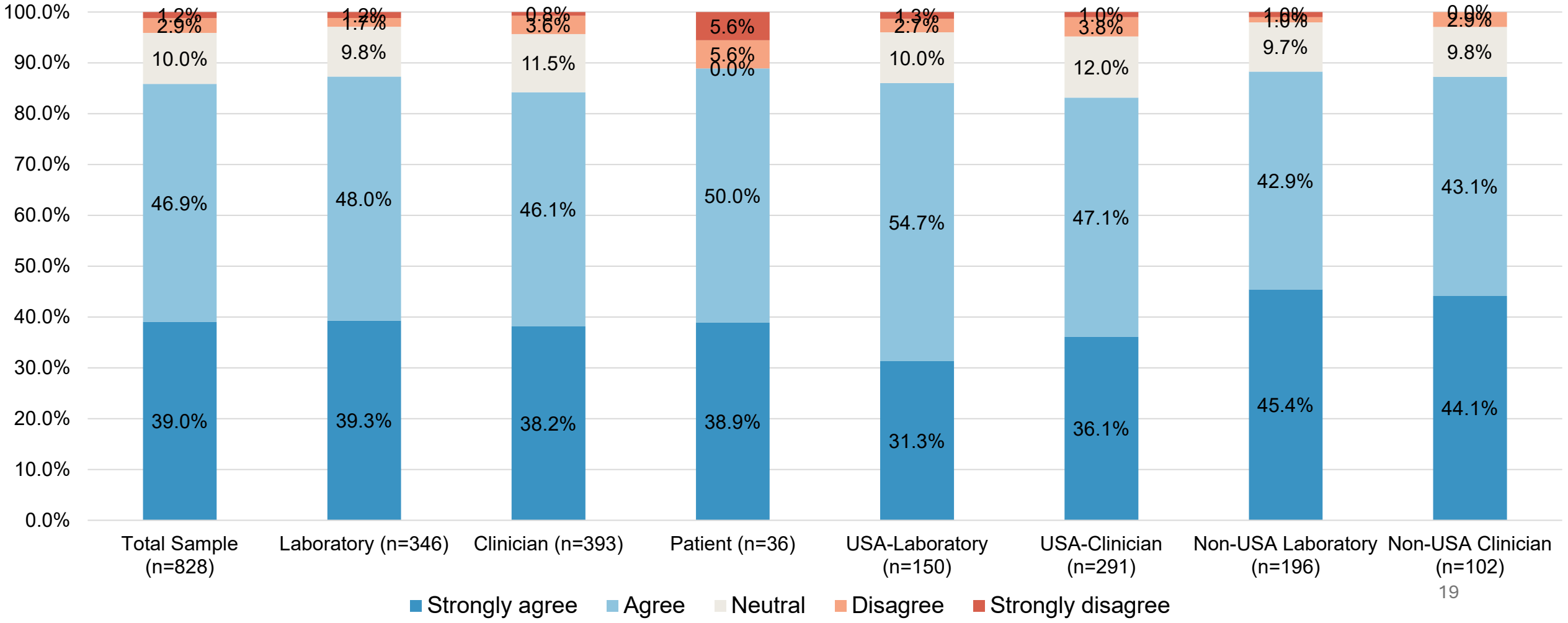
Laboratories should exclude from reporting or de-emphasize (e.g. move to a separate section or supplement) VUS-low variants on genetic testing reports unless there is a strong gene to phenotype match.



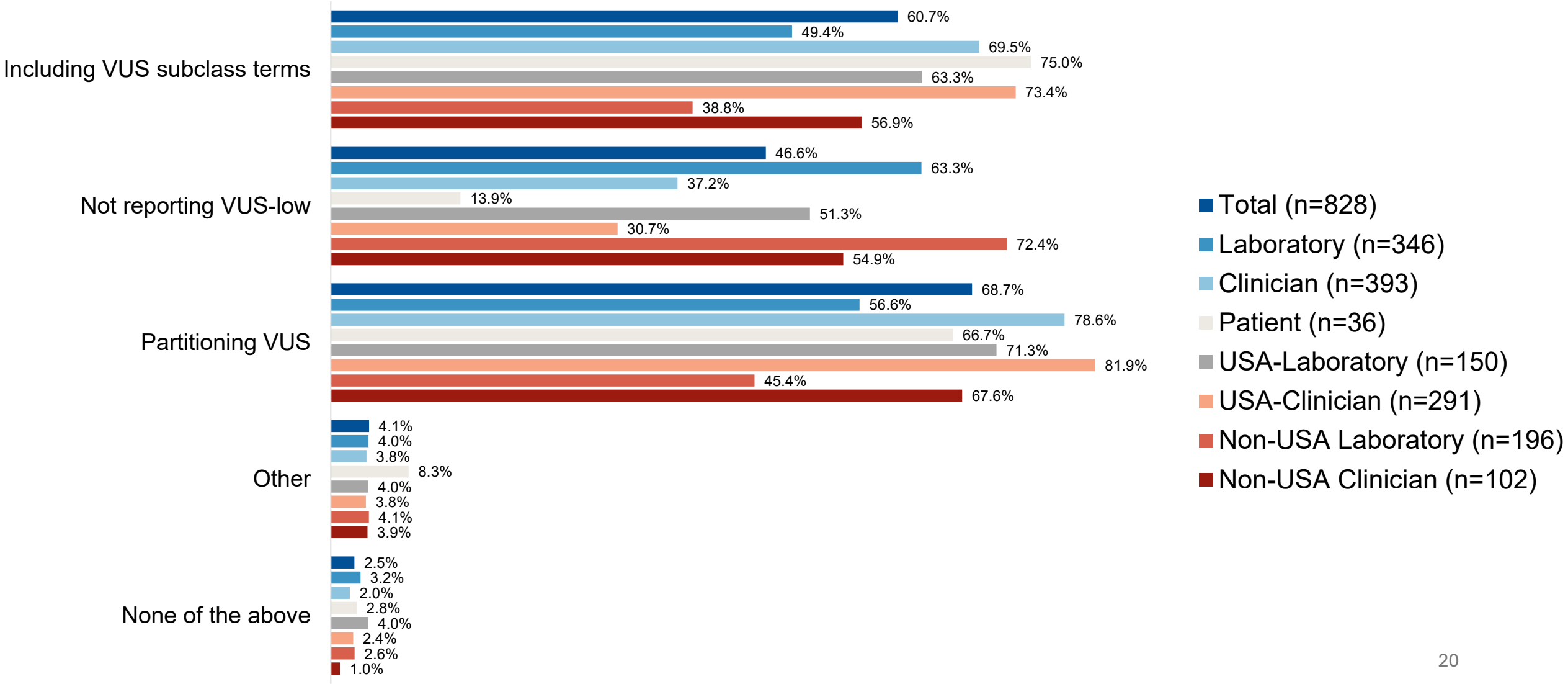
Which of the following scenarios should a laboratory report variants classified as **VUS-high**?



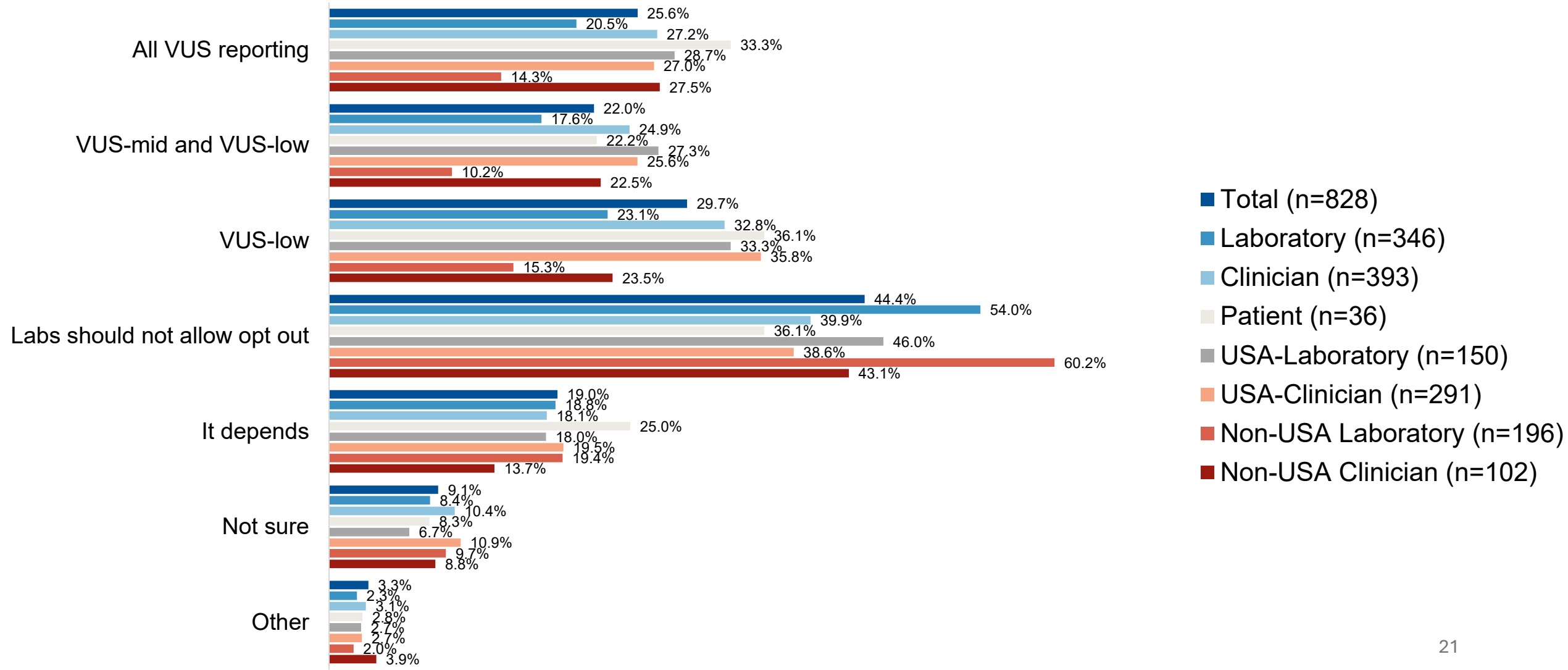
For inconclusive reports, laboratories should consider methods to bring the clinicians' and patients' attention to VUS that most likely explain the phenotype or family history and reduce attention on those VUS that are unlikely to be causal.



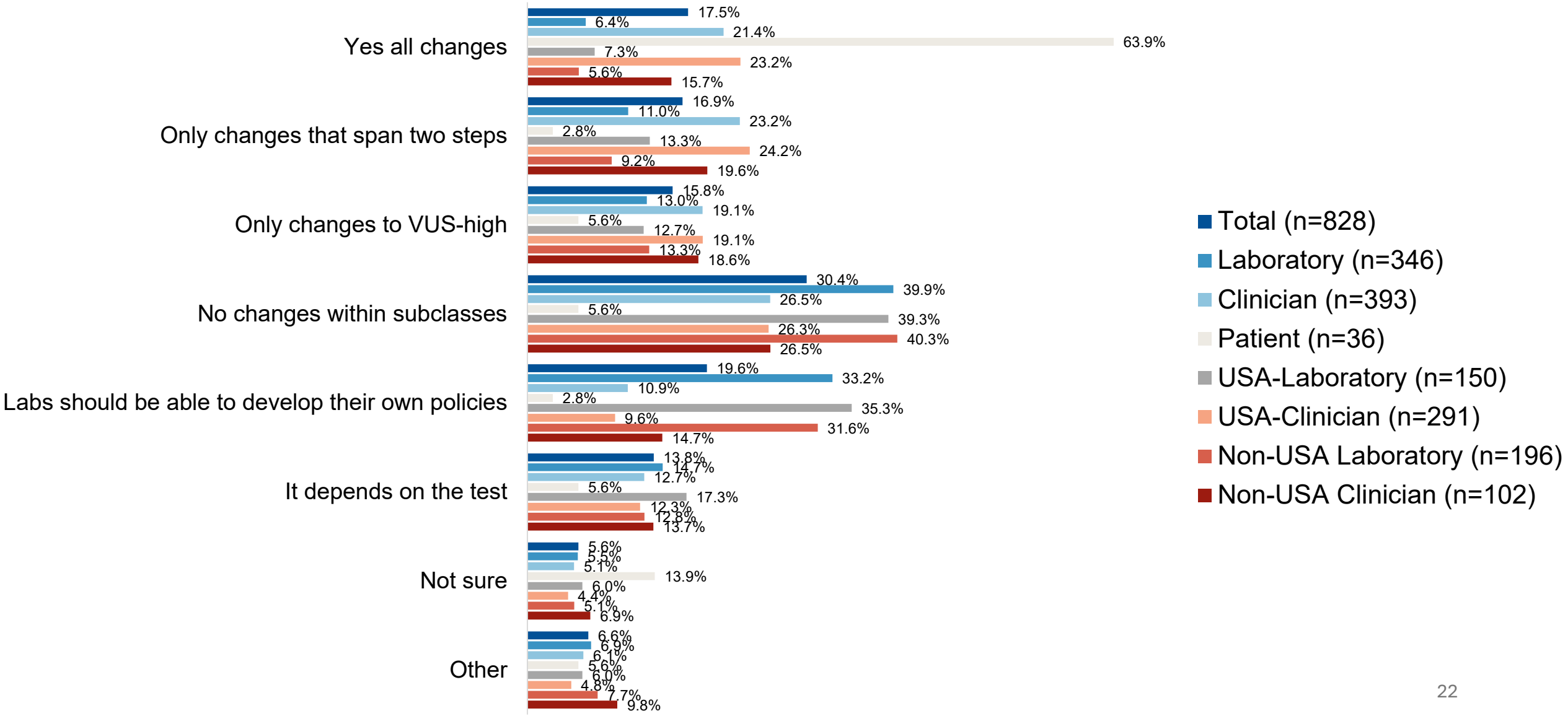
Which of the following methods would be appropriate for **de-emphasizing VUS** that are less likely to explain the patient's phenotype.



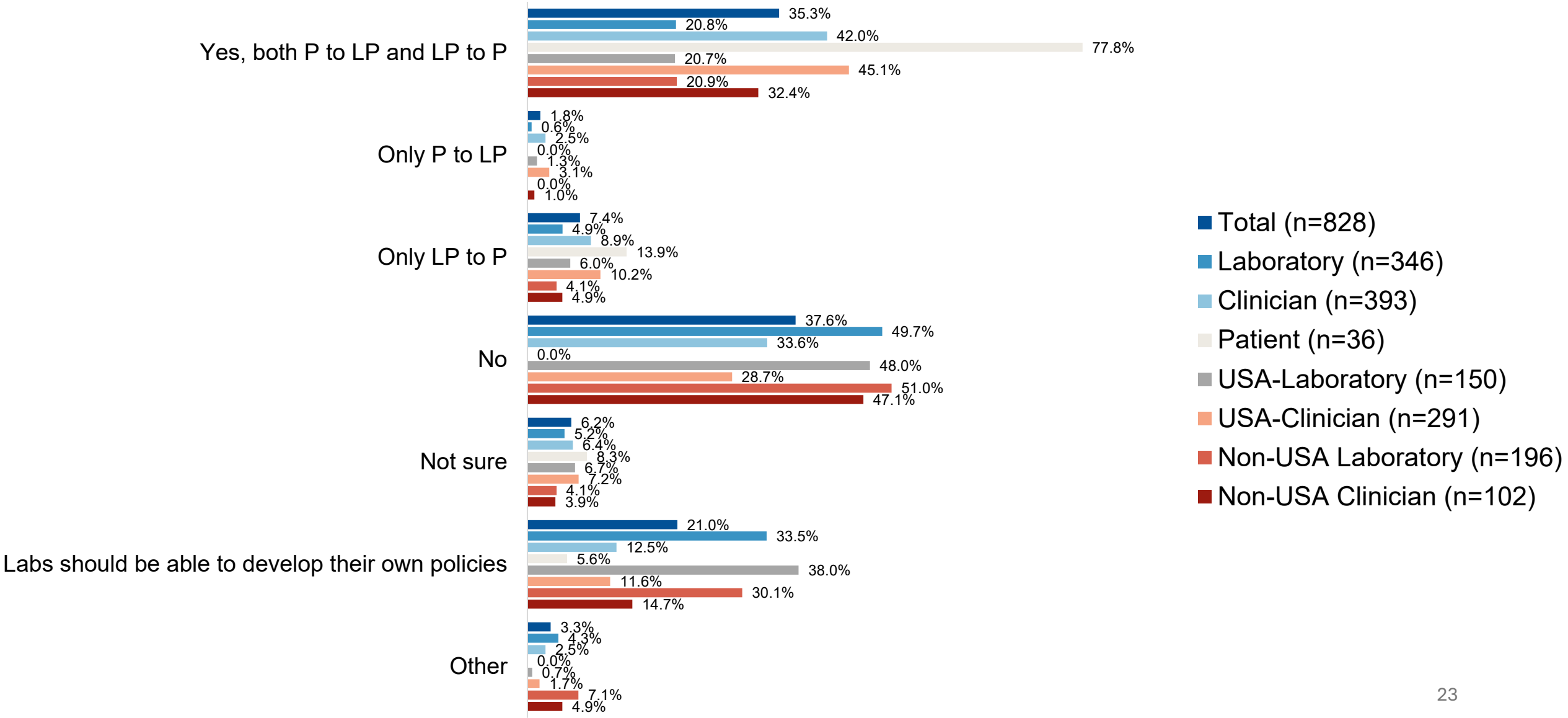
Laboratories should allow patients to **opt out** of which of the following (Note: You may select more than one option to be provided to the patient):



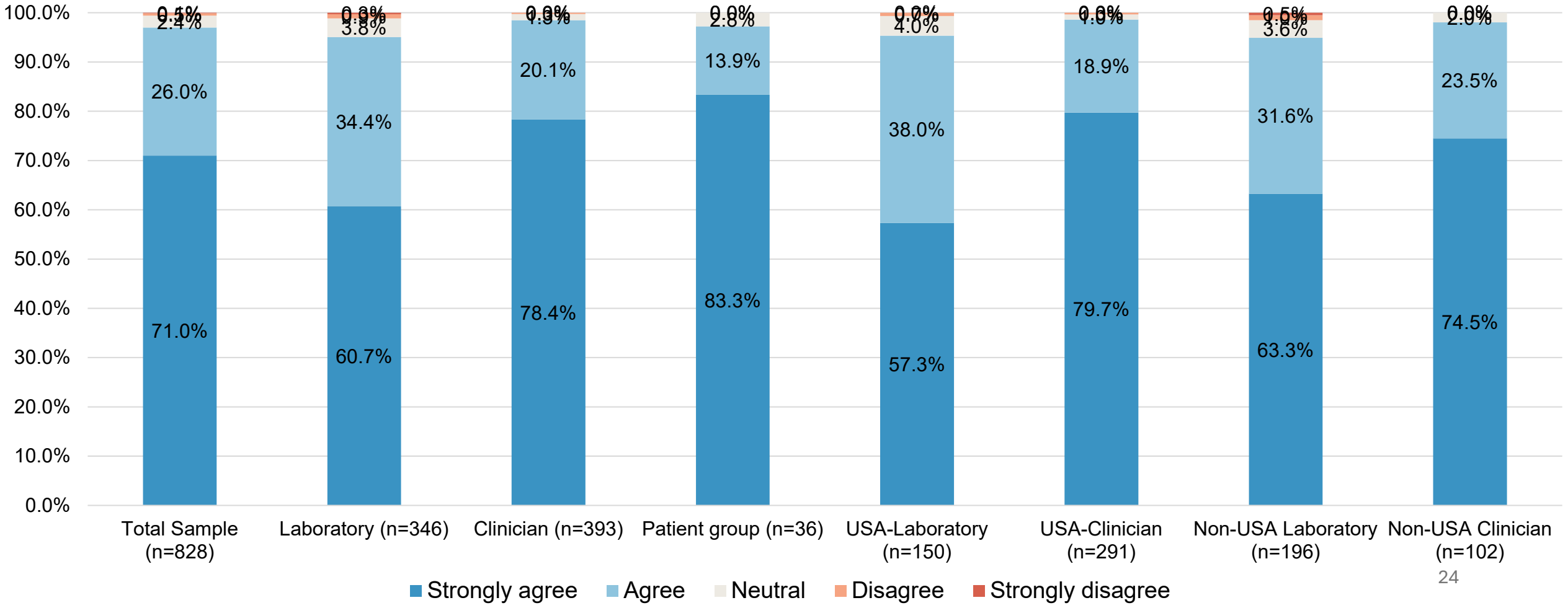
Should updates be sent to clinicians for variant **reclassifications** between the categories of **VUS-low, VUS-mid and VUS-high**?



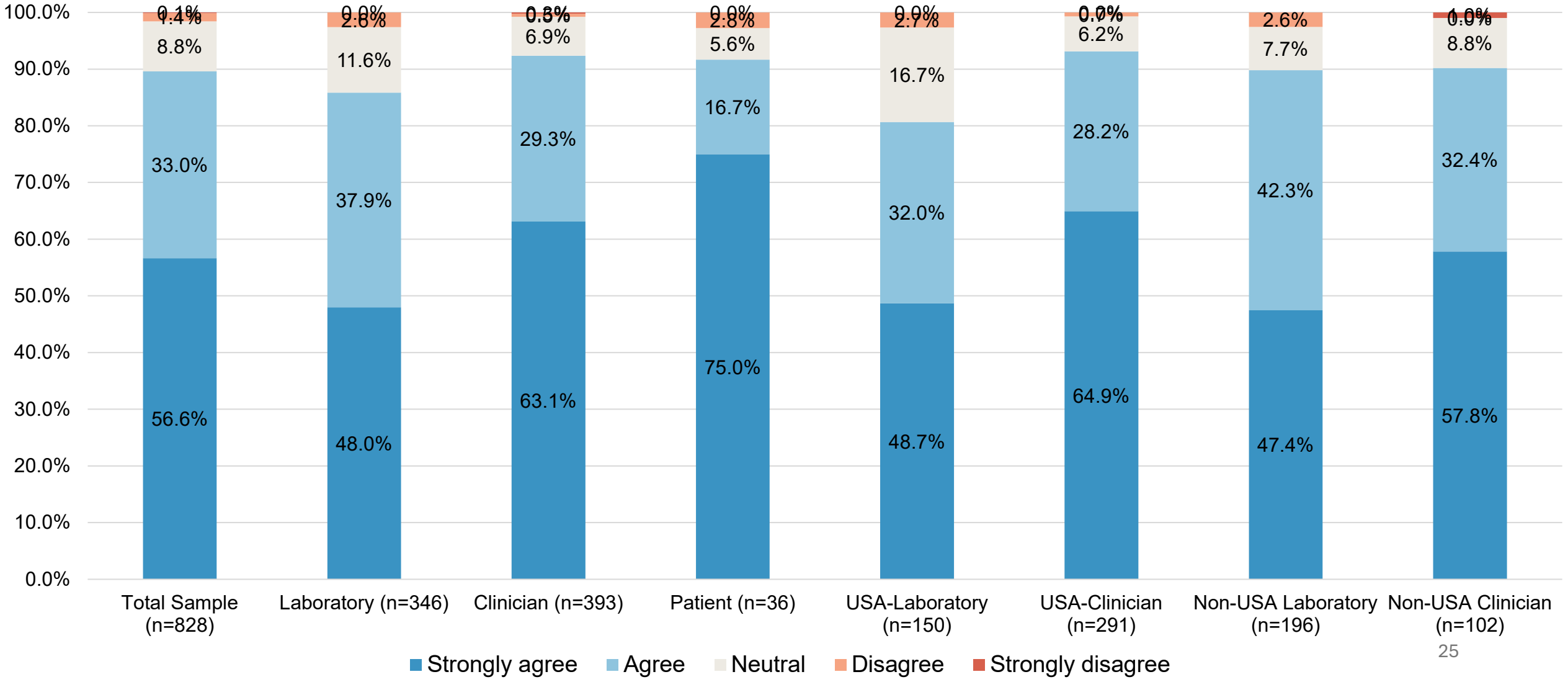
Should variant reclassifications between the categories of **pathogenic** and **likely pathogenic** be sent to clinicians via updated reports?



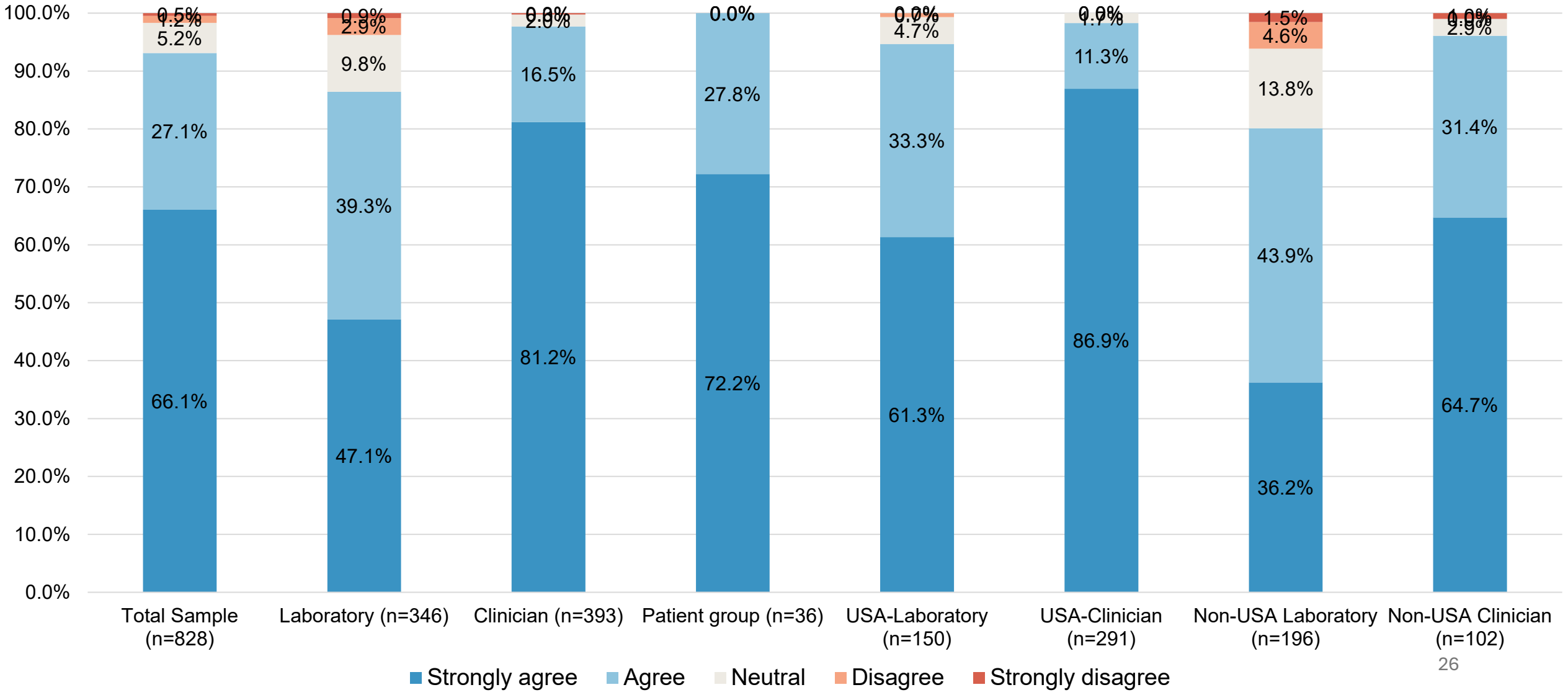
Laboratories are encouraged to include specific follow-up recommendations on genetic testing reports for gathering evidence, especially if it is likely to change the variant classification. For example, laboratories should note when parental testing is recommended to determine de novo occurrence if it will move the variant from VUS to pathogenic.



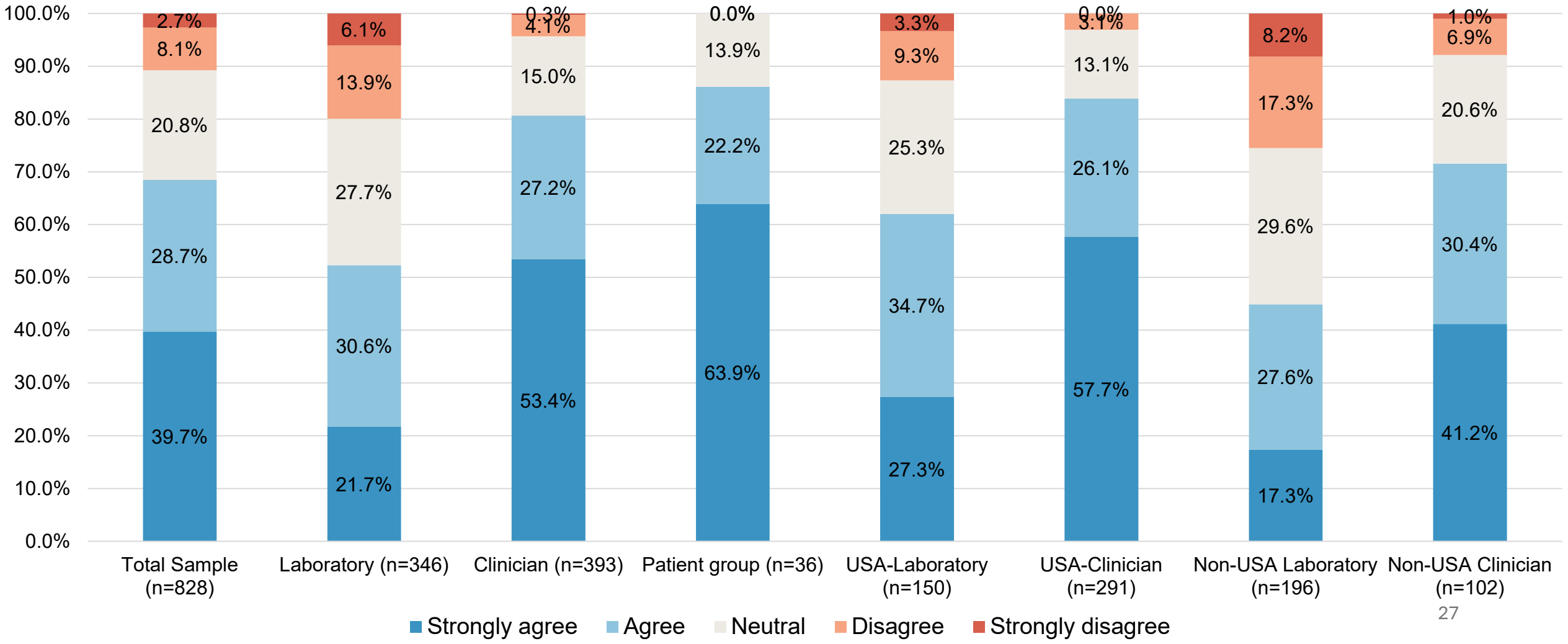
Reports should request that any findings or results obtained after reporting (e.g. additional clinical testing or phenotyping, segregation results from another lab, etc) that are likely to lead to variant reclassification be relayed back to the lab.



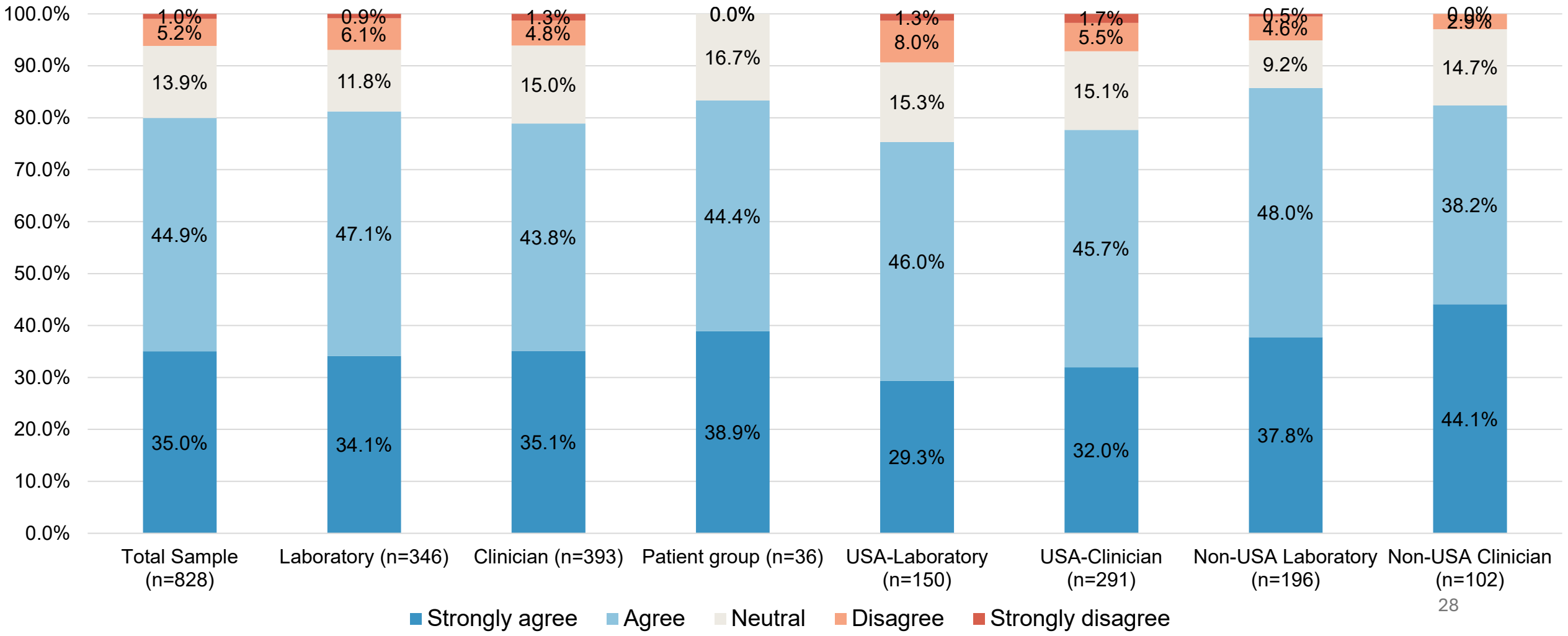
Laboratories should submit variant classifications to ClinVar for variants that **are included** on a clinical report.



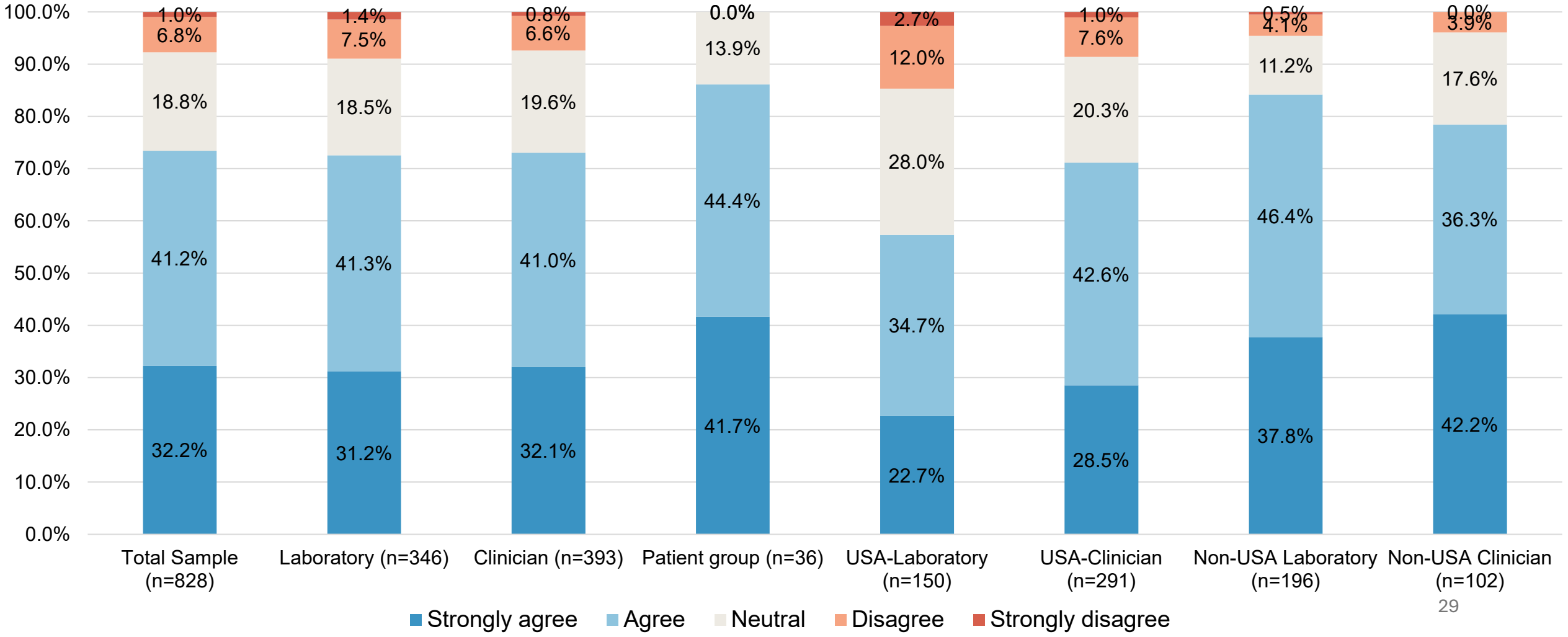
Laboratories should submit variant classifications to ClinVar on variants classified but **not reported** (e.g VUS, LB, B, or LP/P not reported due to gene to phenotype mismatch).



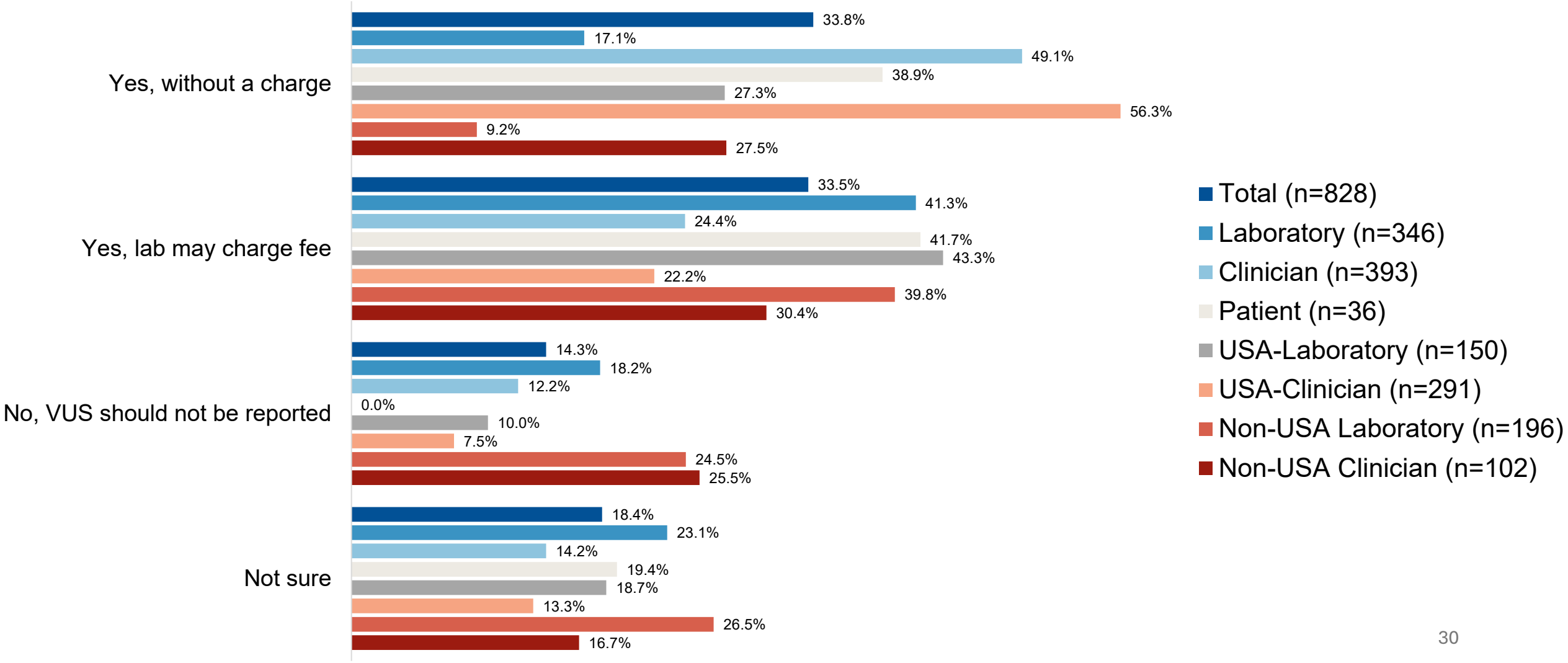
In **genome or exome sequencing**, laboratories should define whether reported variant(s) would be expected to explain the phenotype based on the level of gene-to-phenotype match.



In **multi-gene panel testing**, laboratories should define whether a reported variant would be expected to explain the phenotype (if provided), based on the level of gene-to-phenotype match.



If initial carrier testing was not performed through partner-based analysis, but testing for both partners was performed in a single laboratory, requests to this laboratory to re-examine results with consideration of the current reproductive partners' reports (i.e. to identify the presence of VUS in the same gene) should be supported.



The principles for reporting of VUS in clinical testing should also apply to research studies returning genetic results to participants with rare diseases, provided the IRB protocol for the study is active.