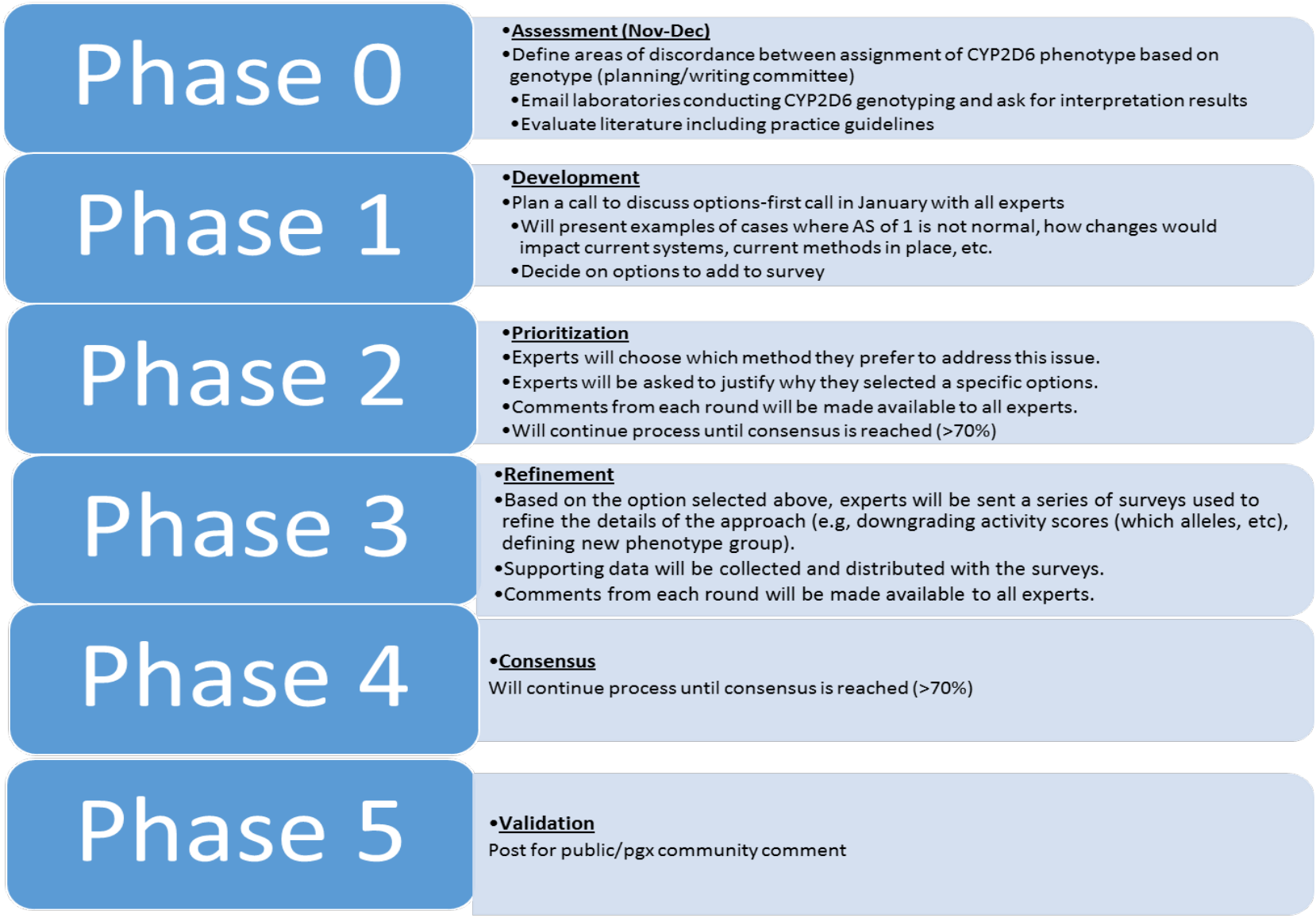
CYP2D6 Genotype to Phenotype Standardization Project

Survey 1 Results

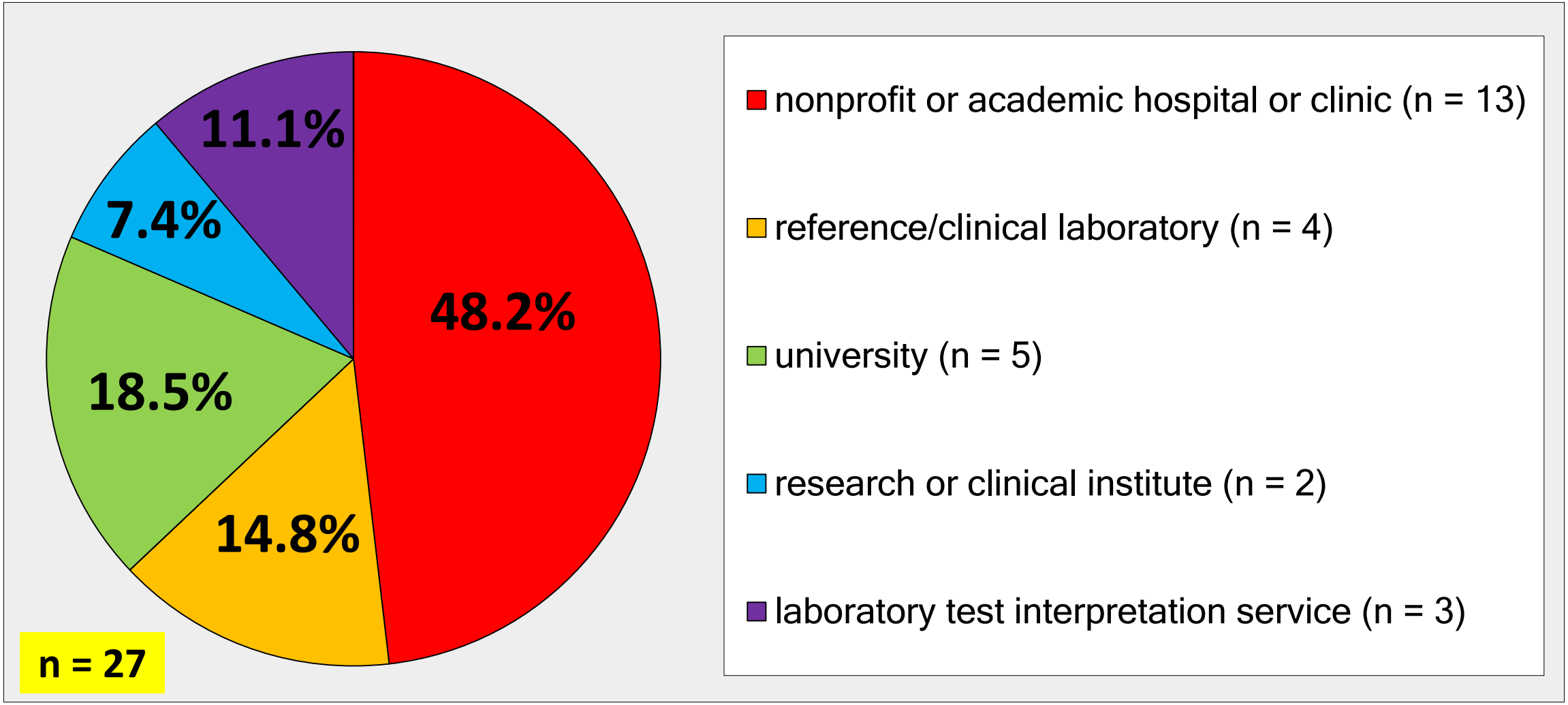
Project Objectives

- Determine a strategy for defining CYP2D6 phenotype based on genotype using a modified Delphi method.

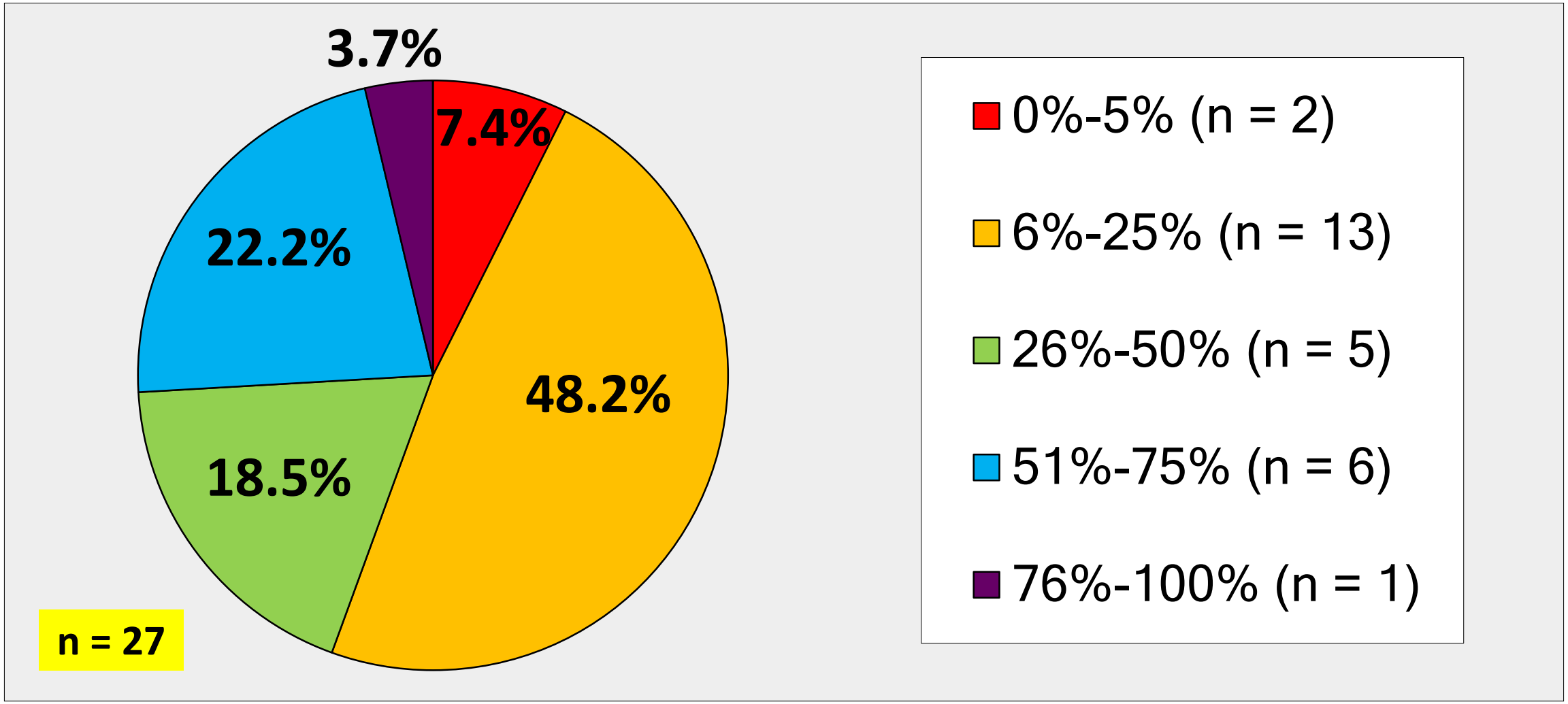
- Standardize phenotype definitions across CPIC and DPWG guideline and external groups.


Phase 0
•Assessment (Nov-Dec)
•Define areas of discordance between assignment of CYP2D6 phenotype based on genotype (planning/writing committee)
•Email laboratories conducting CYP2D6 genotyping and ask for interpretation results
•Evaluate literature including practice guidelines
Phase 1
•Development
•Plan a call to discuss options-first call in January with all experts
•Will present examples of cases where AS of 1 is not normal, how changes would impact current systems, current methods in place, etc.
•Decide on options to add to survey
Phase 2
•Prioritization
•Experts will choose which method they prefer to address this issue.
•Experts will be asked to justify why they selected a specific options.
•Comments from each round will be made available to all experts.
•Will continue process until consensus is reached (>70%)
Phase 3
•Refinement
•Based on the option selected above, experts will be sent a series of surveys used to refine the details of the approach (e.g, downgrading activity scores (which alleles, etc), defining new phenotype group).
•Supporting data will be collected and distributed with the surveys.
•Comments from each round will be made available to all experts.
Phase 4
•Consensus
Will continue process until consensus is reached (>70%)
Phase 5
•Validation
Post for public/pgx community comment

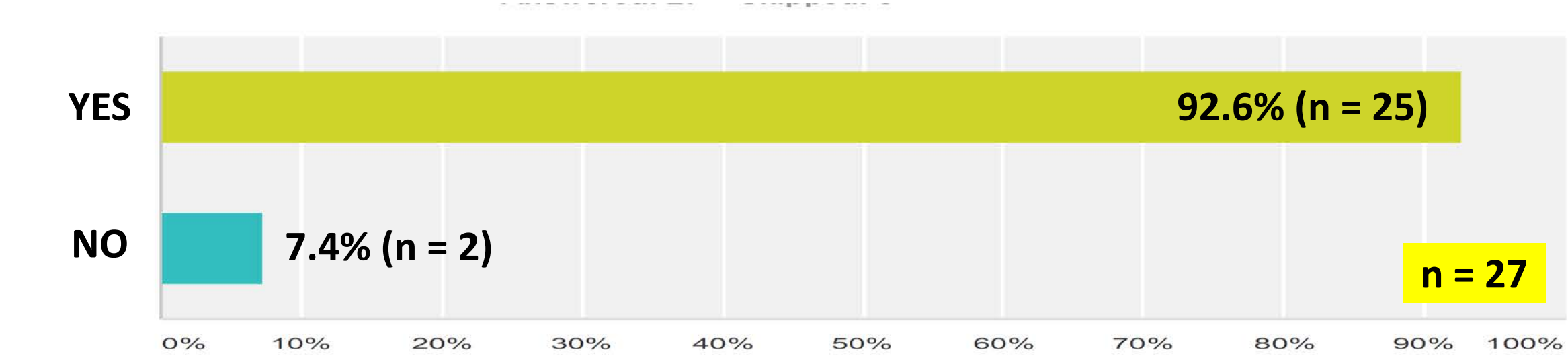
Demographics: Workplace setting



Demographics: % of work involving CYP2D6



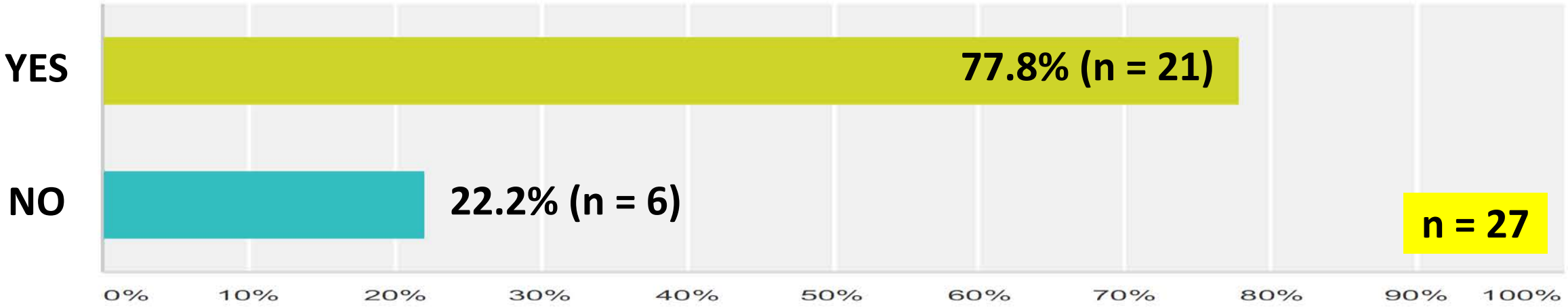
Q1: Clinically significant difference between AS 1 and 2?



Select comments:

- Substrate-specific
- Protein expression as well as functional activity is significantly reduced in AS 1 vs. AS 2
- Definitely PK differences
- PK differences may or may not equate to clinical differences (drug-specific – depends on therapeutic index)
- Strongest difference between *10/*10 and *1/*1 (difference may not exist if *10 is not included in analysis)
- Appears to be difference when *10 included in analysis, but not in studies that do not include *10
- AS 1 may be more prone to interactions with CYP2D6 inhibitor vs. AS 2
- If difference wasn’t found, it was due to small sample size

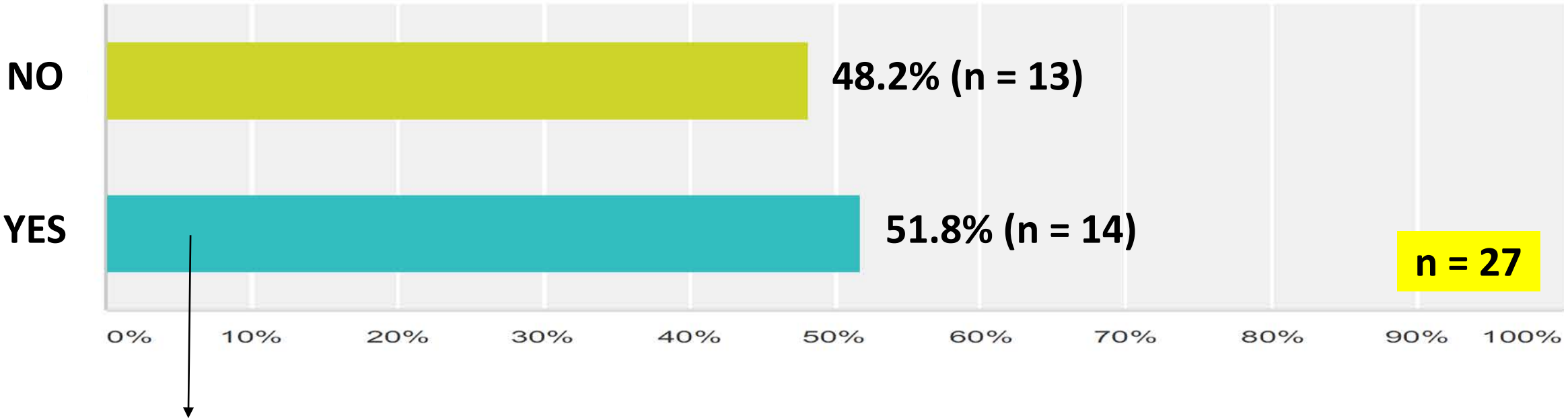
Q2: Clinically significant difference between AS 0.5 and 1?



Select comments:

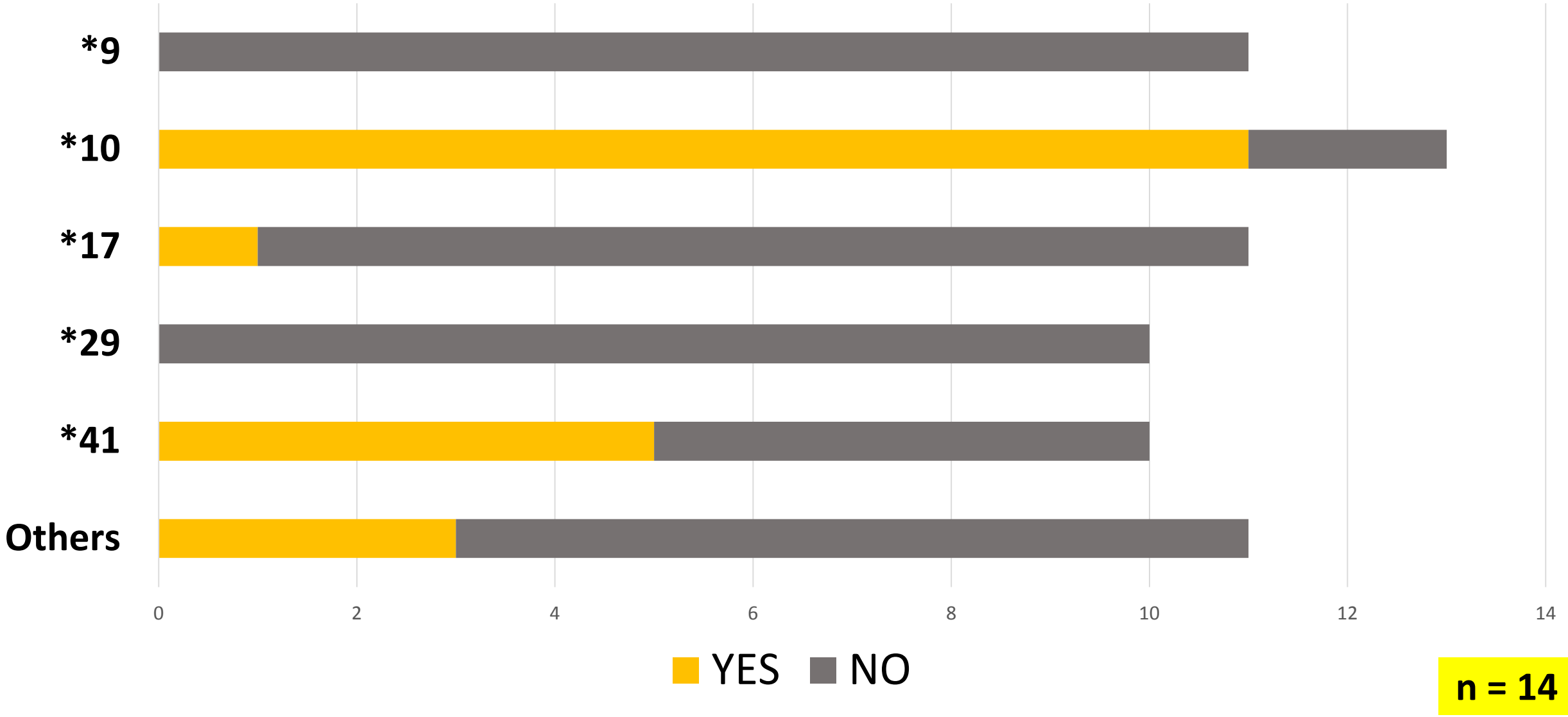
- Substrate-specific
- Difficult to determine from available data – need more research
- Studies that show a difference have a larger sample size than studies that don't
- Less data to support difference
- May be statistical difference but likely no clinical difference
- Best to distinguish between the two to account for the cases where the difference may be relevant
- Recommend keeping phenotypes as detailed as possible to avoid discrepancies between studies that can complicate interpretation when various genotype combinations are pooled in same phenotype

Q3: Downgrade certain alleles from AS 0.5 to AS 0.25?

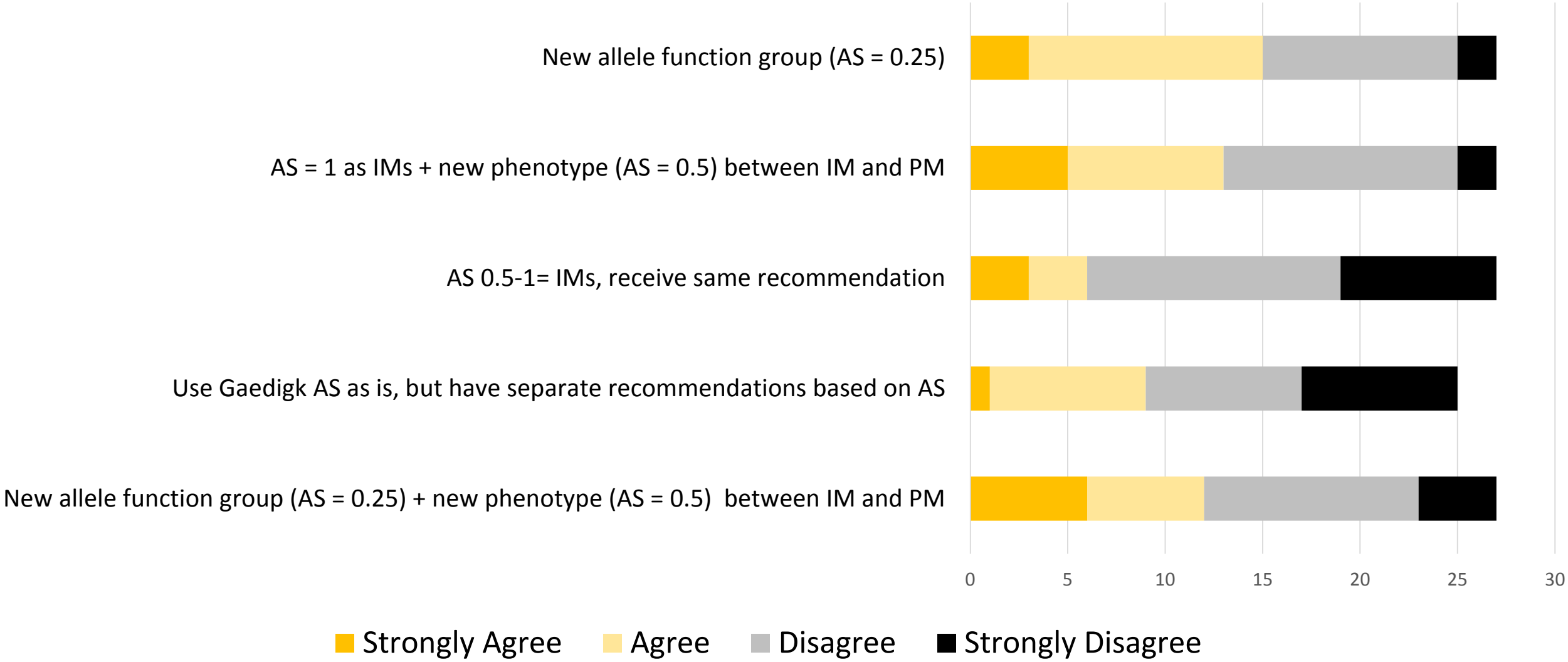


Participants who believe certain alleles should be downgraded were prompted to answer the following question about which alleles should be classified as AS 0.25

Q4: Which alleles should be downgraded to AS 0.25?



Q5: Which method to convert genotype to phenotype?



Last call

- Allele Activity score vs Percentage Activity

Next steps

- Survey 2: Will focus on options where more than 40% agreed:
  - Working with DPWG to come up with recommendations to bring to the group.