Morning breakout session - Grace Pendlebury - Shariant platform & somatic discordance calculation

Participants: Alex Wagner, Andrew Bredemeyer, Daniel Puthawala, Grace Pendlebury, Guoli Sun, Huan Mo, Jason Saliba, Laveniya Satgunaseelan, Mallery Tucker, Mrinal Thomas, Obi Griffith and Yasmeen Kurdi

- Shariant platform allows for group curation and triage for oncogenicity and clinical significance classification
- Discordance resolution discussions are part of this process
- Common problem: how do labs export content in a standardized way
- **Open question:** how important is this?
- Answer: very important. Sharing isn't the issue, there is a data standards barrier. And clinicians want to see the evidence and decision making provenance to reuse it
    - Interpretation/curation software frequently don't support all the necessary fields, so there's a high effort for labs to do development required to discretely send evidence for their somatic classifications (for many labs, it would be a manual entry/submission, which no one has time for).
- Some progress in this space exists: GKS frameworks driving ClinGen somatic submissions to ClinVar; documentation on this framework for use in Shariant requested
- **What is needed:** broader sharing of somatic variant data, pressure on commercial laboratories via insurance reimbursement (analogous to germline)
- Last year survey: 80% of Australian cancer labs are doing both oncogenicity and clinical significance classification
- **Helpful steps towards this goal:**
    - Standardizing and popularizing evidence code strings for submission to ClinVar
    - Promoting submissions that capture clinical significance type (predictive / prognostic / diagnostic / therapeutic) alongside classification rating (Tier I / II)
    - Shariant can copy their production database into test environment to internally evaluate changes; could investigate use of hypothes.is to annotate evidence lines like clinical trials
    - Development of new committees for different assertion types: therapeutic response, diagnostic, prognostic where AMP/ASCO guidelines may benefit from more granularity
    - Some carrot or stick to encourage annotation/classification sharing to, eg: ClinVar.
- Shariant has split out oncogenicity / pathogenicity, good in some ways, but bad for identifying potential conflicts across these classification frameworks
- Pathologists are highly dependent on the WHO Classifications; but these books lack sufficient specificity to confidently classify specific genomic alterations (liability issue)
- NCCN: Variant definitions in the inclusion criteria for clinical trials
- Key challenge: how to accomplish this without adding substantial burden to variant scientists / curators (expectation to follow up on medically significant discordance)
- Variant Allele Frequency (VAF) is a field that is strongly recommended for capture by Shariant, especially for hematopoietic cases.
- Any discussion with Qiagen about interpretation data (is this the QCI interpretation platform? No.)

- Begin with consultation with Shariant labs for opinions on discordance resolution strategies and a potential Australian position to implement, establish a baseline discordance rate for somatic records, similar to the literature ~10% existing for germline. Document process locally.
- No need for ongoing workgroup for discordance resolution
- Work across clinical laboratories with GA4GH/ClinGen joint initiative

- Potential promoting and standardizing sharing mechanisms: CAP Checklists for laboratory accreditation, CAP surveys or proficiency tests (to send out variants to laboratories and get reports back), CAP reporting protocols for molecular pathology reports.
- Intrinsic differences between germline vs somatic mutations for classifications and expertise silos within both disciplines.
- Next step: write up consensus recommendations from this discussion