Why Ambry: Variant Assessment and Classification

EXPERIENCE	A HISTORY OF FIRSTS	• 2001 - First full gene sequencing of CFTR • 2010 - First commercial NSG panel • 2011 - First clinical test for whole exome sequencing • 2012 - First hereiditary cancer panels • 2013 - First *BRCA*-related panels • 2017 - First paired tumor/germline (TumorNext®-*Lynch*) • 2019 - First paired RNA & DNA testing for hereditary cancer (RNAinsight®) • 2021 - First to offer the most comprehensive coverage (up to 91 genes) for RNA analysis

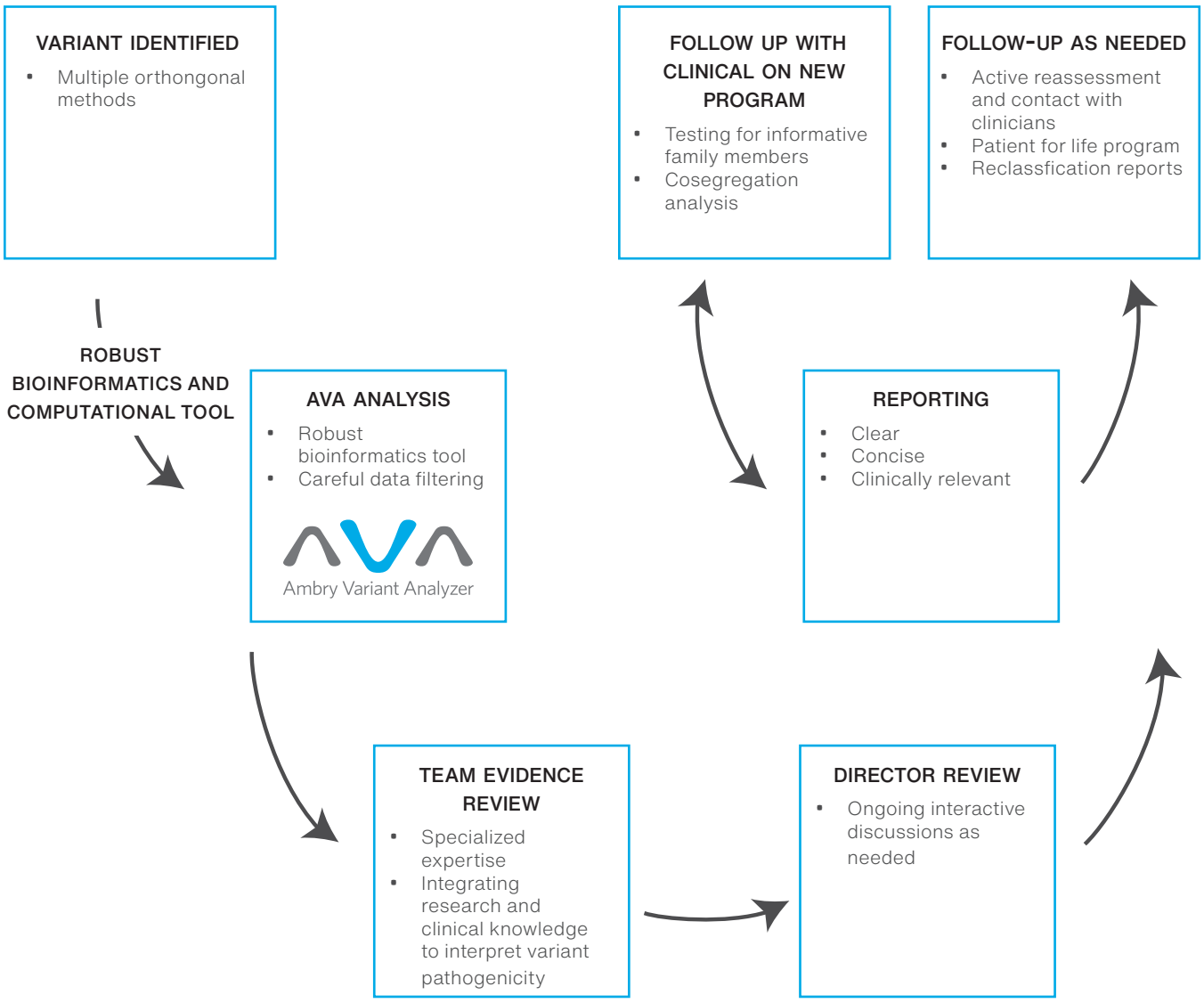
ANALYTICS	AMBRY VARIANT ANALYZER (AVA)	• Proprietary in-house bioinformatics and reporting tool
		  • Integrates with Ambry's large genetics and phenotype knowledge database
		  • Constantly updated with current and clinically relevant information from publications, research, and databases

EXPERTISE	ROBUST, OFFERING CLARITY	• Interdisciplinary Variant Assessment Team of MD and PhD laboratory directors, biostatisticians/bioinformaticians, structural biologists, variant scientists, genetic counselors (https://www.ambrygen.com/science/ambrys-translational-genomics-atg-lab)
		• Specialized expertise in subspecialties (e.g. nonsense mediated decay, protein modeling, RNA, and splicing)
		• Gold-standard variant classification: combination of Ambry expertise with ACMG-AMP guidelines and over 15 years of genetic testing
		  • Classification based on combination of all available evidence
		  • *in silico* and predictive models never used as only line of evidence

FOLLOW-UP	RECLASSIFICATION EFFORTS	• Reclassification efforts help lower VUS rates
		  • Overall Inconclusive rate by 12/31/21 was 20.49%
		  • BRCA1 VUS: 0.83%
		  • BRCA2 VUS 1.64%
		• Our Family Studies Program can offer complimentary VUS analysis in informative families to help offer a clear answer and:
		  • Determine if genetic change is de novo or familial
		  • Understand disease segregation
		• Over 200 genes characterized yearly (cross reference with new variant assessment deck)
		  • Regular reassessment of variant data incorporates emerging evidence and classification
		• Reclassification reports sent to all ordering clinicians if/when classification changes in any direction (e.g. VUS—>benign, VUS—>pathogenic)

SECURE DATA SHARING & COLLABORATION	IMPROVING PATIENT CARE	• Historical and ongoing secure data sharing
		  • Launched AmbryShare (AmbryShare.com) in 2016, which freely shares anonymized aggregate vital genomic data from 10,000+ consented patients with breast and/or ovarian cancer -- program is ongoing across all disease states
		  • As of Jan 2023 we have 223179 submissions in ClinVar
		• Worldwide collaborations (listed at https://www.ambrygen.com/science/collaborations)
		• Scientific presentations, peer-reviewed publications, educational webinars (complete listing at https://www.ambrygen.com/science/collaborations)

Overview of Our Variant Assessment and Classification Process*



- Leading the industry with next generation sequencing (NGS) experience
- Custom, in-house bioinformatics tool
- Dedicated Variant Assessment Team with specialized expertise
- In line with ACMG-AMP standards and guidelines (Richards S, et al., Genetics in Medicine, May 2015)
- Clear, concise, clinically relevant reporting
- Available Board-certified laboratory staff to support you at any point
- Active reassessment of variants to help you find the answer

*This process may differ slightly for ExomeNext variant assessment and classification

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