# Request for ClinGen Expert Panel Designation for Submissions to ClinVar

| Submitter Information | |
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| **Full Name of Submitting Source**: RASopathy Expert Panel | |
| **Acronym or other brief name for ClinVar data display**: RAS Expert | |
| **Expert Panel Member responsible for submission**:<br>Lisa M. Vincent | |
| **Email address**: lvincent@genedx.com | **Phone**: 301-519-2100 x6224 |
| **Expert Panel Coordinator and email address: Bradley Williams (bwilliams@genedx.com)** | |

## Expert Panel Submission Details

### 1. Scope of Work

**Describe the scope of work of the Expert Panel (disease areas and genes being addressed).**

The ClinGen RASopathy Expert Panel (RAS EP) consists of eleven (11) individuals with diverse qualifications including clinical medical geneticists, clinical research scientists, and clinical laboratory diagnosticians as well as an assigned ClinGen biocurator. In addition, representatives from multiple other clinical diagnostic laboratories contribute to curating clinical laboratory case level data and to discussions regarding variant classifications. Taken together, our members and support team span over eleven (11) institutions and encourage participation by the community.

The RAS EP's goals aim to support and perform gene curation and variant classifications using tailored ACMG/AMP criteria in the following genes: *BRAF, HRAS, KRAS, MAP2K1, MAP2K2, PTPN11, RAF1, SHOC2, SOS1* in relation to the disorders within the RASopathy disorder spectrum, which include Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML, formerly known as LEOPARD syndrome), Costello syndrome, Cardio-facio-cutaneous (CFC) syndrome and other Noonan-like disorders.

## 2. Composition of the Expert Panel

*Expert Panels within ClinGen are expected to represent the diversity of expertise in the field, including all major areas of expertise (clinical, diagnostic laboratory, and basic research). Membership should include representation from three or more institutions and will encompass disease/gene expert members as well as biocurators. Biocurators do not have to be gene/disease experts and will be primarily responsible for assembling the available evidence for subsequent expert member review. For role, suggested examples include: primary biocurator, expert reviewer, etc.*

**Member List**

| Name | Institution | Area and Type of Expertise | Role |
|---|---|---|---|
| Hélène Cavé, PharmD, PhD | Département de Génétique, Hôpital Robert Debré and Institut Universitaire d'Hématologie, Université Paris Diderot, Paris-Sorbonne-Cité | Clinical laboratory, Molecular genetic testing; Pediatric Genetics; Research, RASopathies | Expert Reviewer |
| Brandon Cushman | Partners Healthcare, Laboratory for Molecular Medicine | ClinGen Biocuration | Primary ClinGen EP Biocurator |
| Mitchell Dillon, MS, CGC | Icahn School of Medicine at Mount Sinai, Molecular Genetic Testing Laboratory | Clinical laboratory, Molecular genetic testing | Subgroup leader; Expert Reviewer |
| Bruce D. Gelb, MD | Icahn School of Medicine at Mount Sinai | Clinical diagnostician, Pediatric Cardiology; Research, Disorders with congenital heart defects | Co-Chair; Subgroup leader; Expert Reviewer |
| Karen W. Gripp, MD, FAAP, FACMG | Nemours/Alfred I. duPont Hospital for Children | Clinical diagnostician, Pediatric Genetics; Research, Costello Syndrome, RASopathies and multiple congenital anomalies | Expert Reviewer |
| Jennifer A. Lee, PhD, FACMG | Greenwood GeneticCenter | Clinical laboratory. Molecular genetic testing | Subgroup leader; Expert Reviewer |
| Heather Mason-Suares PhD, FACMG | Partners Healthcare, Laboratory for Molecular Medicine | Clinical laboratory, Molecular genetic testing; Research, RASopathies | Subgroup leader; Expert Reviewer |
| Katherine A. Rauen, MD, PhD | UC Davis Children's Hospital | Clinical diagnostician, Clinical Diagnostician, Clinical Genetics; RASopathy Research, Cardio-facio-cutaneous Syndrome, Costello Syndrome, RASopathies, Multiple Congenital Anomalies | Expert Reviewer |
| Lisa M. Vincent PhD, FACMG | GeneDx | Clinical laboratory. Molecular genetic testing | Co-Chair; Subgroup leader; Expert Reviewer |
| Bradley Williams, MS, CGC | GeneDx | Clinical laboratory. Molecular genetic testing | Subgroup leader; Expert Reviewer |

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| Martin Zenker, MD | Institute of Human Genetics, University Hospital Magdeburg, Germany | Clinical diagnostician, Pediatric Genetics; Molecular genetic testing; Research, RASopathies | Expert Reviewer |

Additionally, the ClinGen RAS EP welcomes representatives from multiple other clinical diagnostic laboratories who contribute to curating clinical laboratory case level data and to discussions regarding variant classifications.

(Insert additional page if needed)

## 3. Conflict of Interest Management

*Expert Panels within ClinGen are expected to represent the diversity of expertise in the field and should be composed of a sufficient number of eligible expert reviewers to address academic and financial conflicts of interest that may arise.*

- *Academic COI: Authors of literature about relevant variants may serve on the Expert Panel and are welcome to voice their opinion, but should not be the major arbiter of a variant classification when there is limited data available and it was provided by that individual or the individual's lab group.*
- *Financial COI: Commercial entities may participate on the Expert Panel, but should not be the major arbiter of a variant classification when there is limited data available and it was provided by that entity.*
- *No special measures are needed if there is group consensus on a variant classification; however, if a vote is needed, those with relevant conflicts of interest should recuse themselves.*
- *All conflicts will be declared publicly on the clinicalgenome.org website and reported in publications as appropriate.*

**Describe any other specific processes for managing potential conflicts of interest, if any.**

Each EP co-chair is expected to receive funds under a contractor status through Clinical Genome Resource grant (TBD; September 2017) for the first two years for organizing and leading this expert panel. There is no other direct compensation for participation in this expert panel nor are experts expected to have any financial gain from participation in this panel. This expert panel and additional members span eleven (11) different institutions with no implicit financial connections and all members are expected to contribute and approve all final actions and decisions of the panel relating to the standard duties expected of a ClinGen expert panel including, but not limited to, variant classifications and gene curation. Any potential, perceived, or implied financial conflicts of interest should be reported to the panel for discussion of impact. If needed, the expert panel will submit any potential financial conflicts to the ClinGen steering committee. In addition, all work from this EP will be represented as work completed within the ClinGen initiative. Any EP member or the community should submit any information pertaining to any potential non-reported COI to the ClinGen steering committee at their own independent discretion.

## 4. ACMG guideline specifications

*ClinGen Expert Panels will use the ACMG/AMP variant assessment criteria as their starting point for a framework to adjudicate Mendelian variants according to the five class criteria (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign). The Expert Panel process will entail reviewing the evidence types and making gene-specific specifications to the ACMG/AMP guidelines, including consultation with the Genomic Variant WG and the Sequence Variant Interpretation WG in order to ensure harmonization of approaches across different expert panels. ClinGen Expert panels are expected to follow milestones as described in the EP toolkit.*

**Provide the gene-optimized rules for variant classification designed by the Expert Panel as an appendix. Documentation will be made publicly available and could consist of a manuscript pre-print or published manuscript. The following items must be included in the submitted material:**

- **A description of the specified ACMG/AMP guidelines for the gene(s) of interest, including evidence and rationale to support the rule specifications.**
- **A description of how your rules were validated with known variants.**

See attached document entitled “RAS EP_ACMGCriteriaV1_final_6.29.17.doc”. Additionally, the document entitled “RAS EP_ACMGCriteraV1_SupplementalMaterial_final.xls” contains a summary view of our ACMG rule adjustments, the justification and background for allele frequency adjustments, and curated gene and variant information.

## 5. Model ClinVar submission

*ClinGen Expert Panels are expected to make submissions to ClinVar through the ClinGen Variant Curation Interface (VCI) in order to standardize the content across expert panels.*

**Please provide a sample list of classified variants curated in the VCI or attached in a spreadsheet.**

See attached document entitled “RAS EP_ACMGCriteraV1_SupplementalMaterial_final.xls” that contains over 100 variants classified using the RAS EP ACMG/AMP adjusted guidelines.

## 6. Standard Operating Procedure for variant curation and review

*ClinGen Expert Panels are expected to develop work schedules, review and resolve differences in interpretation, and provide standard procedures for variant assessment.*

**Standard Operating Procedures:**

- **Meeting/call frequency:** Monthly

- **Curation/expert review/finalization process:**

  ☑ **Version 1: One curator performs data entry and baseline curation; two domain experts perform blinded double review and classification. Discussions with the full EP are triggered if:**

  **a) the experts do not reach consensus,**

  **b) either expert raises concerns regarding the "fit" of a rule, or**

  **c) the strength of functional evidence needs further input.**

  □ **Version 2: Two curators perform independent assessments followed by full EP review and consensus classification.**

  □ **Other**

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- **Describe combinations of rules and evidence sources that could be used to classify any categories of variants (e.g. Benign or Likely Benign) in a batch:**

  To improve efficiency, variants with ExAC filtering allele frequencies greater than or equal to the thresholds set for BA1 (0.05%) and BS1 (0.025%) can be batched for automatic classifications as benign and likely benign, respectively. Auto-classifications will only be performed if the variant has not been associated with a publication (as reflected by the variant's presence in HGMD) or any other moderate or strong pathogenic criteria. Potentially conflicting case-level data will be assessed based on presence of either a likely pathogenic or pathogenic classification by another submitter within ClinVar. Note that computational evidence supporting a deleterious effect will not be considered as contradictory evidence given these are predictions.

- **ClinVar submission schedule:**

  □ **Quarterly**

  ☑ **Twice Yearly**

  **Other**

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## 7. Procedures for variant interpretation reanalysis

*ClinGen Expert Panels are expected to keep their variant interpretations up-to-date and to expedite the re-review of variants that have a conflicting assertion in ClinVar*.

☑ **The Expert Panel will contact the submitter of a newly submitted conflicting assertion in ClinVar from a one star submitter or above and attempt to resolve or address the conflict within 4 months of being notified about the conflict through the VCI.**

**AND**

☑ **The Expert Panel will systematically re-review all VUS classifications within 2 years of the ClinVar submission.**

**AND**

☑ **The Expert Panel will re-review any LP or LB classifications when new evidence is available in the VCI or when requested by the public via the ClinGen website.**

**OR**

☐ **Other**

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