**Request for “Expert Panel” Designation on ClinVar**

**1. Name of Expert Panel (please write out any acronyms):**

***International Society for GastroIntestinal Hereditary Tumors (InSiGHT) – Variant Interpretation Committee (VIC). Full acronym: InSiGHT VIC***

**2. Date form submitted to** [**clinvar@ncbi.nlm.nih.gov**](mailto:clinvar@ncbi.nlm.nih.gov) **: September 2, 2014**

**3. Contact name, institution and email address for one Expert Panel representative who will be the contact person for the ClinGen Executive Committee:**

***Maurizio Genuardi, Institute of Medical Genetics, Catholic University, Rome, Italy; email*** [maurizio.genuardi@unicatt.it](mailto:maurizio.genuardi@unicatt.it)

***Role: VIC chairperson***

**4. Please provide member names, type of expertise, e.g. clinical, clinical laboratory, bioinformatic or research and institutional affiliation of the Expert Panel members using the table provided. Please note any individuals currently serving in a leadership role e.g. steering committee chairs.**

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| --- | --- | --- | --- |
| **Name** | **Institution** | **Expertise** | **Leadership Role** |
| Kiwamu Akagi | Div. Molecular Diagnosis and Cancer Prevention, Saitama Cancer Center, Saitama, Japan | MD, PhD: Molecular Pathology |  |
| Fahd Al-Mullah | Department of Pathology, Faculty of Medicine, Health Sciences Center, Kuwait University, Safat, Kuwait | BSc, M.B.,Ch.,B., PhD, FRCPE:  Molecular Pathology |  |
| Inge Bernstein | Danish HNPCC Registry, Copenhagen, Denmark | MD, PhD, MHM: Gastrointestinal Surgery |  |
| Bharati Bapat | Department of Lab Medicine and Pathobiology, University of Toronto, Canada | BSc, MSc, PhD: Cancer  Genetics, Molecular Pathology |  |
| Gabriel Capellà | Hereditary Cancer Program. Catalan Institute of Oncology, Barcelona, Spain | MD PhD: Molecular Pathology and Genetic Oncology Research |  |
| Desirée du Sart | Molecular Genetics Lab, Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Melbourne, Australia | PhD: Diagnostic molecular  genetics |  |
| Aurelie Fabre | INSERM UMR S910, Department of  Medical Genetics and Functional  Genomics, Marseille, France | Cancer Genetics Research |  |
| Michael Farrell | Department of Cancer Genetics,  Mater Private Hospital, Dublin,  Ireland | R.G.N., H. Dip. Applied Science,  B.Sc. in Computing, Grad. Dip.  in Oncology Nursing, M. Sc. in  Molecular Medicine: Genetic  counseling |  |
| Susan Farrington | Colon Cancer Genetics Group,  Institute of Genetics and Molecular  Medicine, University of Edinburgh,  Scotland | BSc, PhD: Cancer and  Molecular Genetics Research |  |
| Ian Frayling | Institute of Medical Genetics,  University Hospital of Wales, Cardiff,  UK | MA (Cambridge; Medical  Sciences with Honours in  Biochemistry), MB BChir  (Cambridge), PhD (Manchester:  DNA repair), FRCPath (Clinical  Molecular and Cytogenetics),  FEBLM (Founder Fellow  European Board of Laboratory  Medicine): Molecular Pathology |  |
| Thierry Frebourg | Inserm U614, Faculty of Medicine, Institute for Biomedical Research, University of Rouen, France | PhD: Molecular genetics  diagnostic and research |  |
| Maurizio Genuardi | Institute of Medical Genetics, Catholic University, Rome | MD. Clinical and laboratory genetics | Committee Chair |
| David Goldgar | Department of Dermatology; University of Utah Medical School; Salt Lake City, Utah, U.S. | PhD: Genetic epidemiology |  |
| Marc Greenblatt | University of Vermont; Burlington, Vermont, U.S. | MD: Medical Oncology |  |
| Chris Heinen | Neag Comprehensive Cancer Center & Center for Molecular Medicine, UConn Health Center, Farmington, CT, U.S. | PhD: Cancer Genetics Research  (functional assays) |  |
| Elke Holinski-Feder | University of Munich, Germany | MD, PhD: Diagnostic molecular  genetics |  |
| Maija Kohonen-Corish | Garvan Institute of Medical Research, Sydney, Australia | BSc, MSc, PhD, MHGSA:  Cancer genetics research |  |
| Kristina Lagerstedt-Robinson | Karolinska Institutet, Karolinska Univ Hospital, Stockholm, Sweden | PhD: Diagnostic molecular  genetics |  |
| Suet Yi Leung | Department of Pathology, The University of Hong Kong, Hong Kong, China | MBBS, MD, FRCPath(UK),  FRCPA, FHKAM (Pathology),  FHKCPath: Diagnostic  molecular genetics; Cancer  genetics and genomics;  Molecular pathology |  |
| Finlay Macrae | The Royal Melbourne Hospital and University of Melbourne, Australia | MBBS (Hons1 Monash), MD (Melb), FRACP, FRCP (UK), AGAF: Gastroenterology | InSiGHT Secretary and liaison with InSiGHT Council |
| Alexandra Martins | Inserm U614, Faculty of Medicine, Institute for Biomedical Research, University of Rouen, France | PhD: Diagnostic molecular  genetics, Cancer genetics and  RNA biology research, RNA  splicing assays |  |
| Pal Moller | Section for Inherited Cancer, Department of Medical Genetics; The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway | MD, PhD: Clinical genetics,  Cancer genetics, Genetic  epidemiology |  |
| Monika Morak | University of Munich, Germany | PhD: Cancer genetics research,  splicing and cDNA assays. |  |
| Minna Nystrom | Department of Biosciences, Genetics; University of Helsinki, Finland | PhD Cancer genetics research  (functional assays) |  |
| Paivi Peltomaki | Department of Medical Genetics,  Haartman Institute; University of  Helsinki, Finland | MD, PhD: Cancer genetics  research and InsiGHT database  curator | Database curator |
| Marta Pineda | Hereditary Cancer Program. Catalan Institute of Oncology, Barcelona, Spain | PhD: Diagnostic molecular  genetics |  |
| John-Paul Plazzer | Department of Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Australia | BEng (Comp), GradDip (Bioinf):  Database curator | Database curator |
| Ming Qi | ADINOVO Center for Genetic & Genomic Medicine; The First Affiliated Hospital of Zhejiang University School of Medicine; James Watson Institute of Genomic Sciences, Beijing Genome Institute, China AND University of Rochester Medical Center, NY, USA | PhD, FACMG: Diagnostic  moelcular genetics |  |
| Raj Ramesar | Division of Human Genetics, University of Cape Town, Cape Town, South Africa | PhD: Diagnostic molecular  genetics |  |
| Lene Rasmussen | Center for Healthy Aging,, University of Copenhagen, Denmark | PhD: Cancer genetics research  (functional assays) |  |
| Brigitte Royer-Pokora | Institute of Human Genetics, University of Düsseldorf, Germany | PhD: Diagnostic molecular  genetics and functional assays |  |
| Rodney Scott | Discipline of Medical Genetics, Faculty of Health, University of Newcastle, The Hunter Medical Research Institute, NSW, Australia. | PhD, DSc, FRCPath, FHGSA,  FFSc(RCPA): Cancer genetics,  diagnositic and research |  |
| Rolf Sijmons | Dept of Genetics, University Medical Center Groningen, Groningen, the Netherlands | MD PhD: Clinical genetics | Database curator |
| Amanda Spurdle | Molecular Cancer Epidemiology  QIMR Berghofer Medical Research Institute | PhD: molecular cancer  epidemiology research |  |
| Sean Tavtigian | Huntsman Cancer Institute, Salt Lake City, UT, U.S. | PhD: Cancer genetic research -  bioinformatics |  |
| Bryony Thompson | Molecular Cancer Epidemiology  QIMR Berghofer Medical Research Institute | BSc (Hons), PhD scholar:  cancer genetics research | Database curator |
| Juul Wijnen | Leiden University Medical Centre, The Netherlands | PhD: Diagnostic molecular  Genetics |  |
| Mike Woods | Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland; St. John's, NL, Canada | PhD: Diagnostic molecular  genetics and database curator | Database curator |

**5. One page summary of the process used by the Expert Panel with regard to making clinical assertions for genetic variants. Please note all genes currently under review by this process and any plans for future genes to be evaluated and assertions submitted to ClinVar.**The InSiGHT VIC (Online Methods) was established in 2007 to address discrepancies in the classification of Mismatch Repair (MMR) gene variants lodged in the InSiGHT database. Since March 2011, the VIC has made a concerted effort to develop standardized criteria for variant classifi­cation, employing a modified Delphi consensus process to evaluate current scientific evidence and reach consensus. In line with the Human Variome Project, the IARC classification system1 for variant categorization was adopted for the classification of MMR gene variants.

Briefly, multiple lines of evidence were required for classification, and evidence for each variant had to include data associating the variant with both clinical and functional consequences. The classification rules are based on the following:

- The 5 class system described for quantitative assessment of variant pathogenicity in Plon et al.1, using a multifactorial likelihood model as applied to MMR gene variants2;

- The 5 class system for interpretation of splicing variants and aberrations by Spurdle et al.3;

- The classification of sequence changes according to standard clinical practice – that is, description of variants generally considered pathogenic (clinically relevant in a genetic counselling setting such that germline variant status is used to inform patient and family management) or non-pathogenic (significant evidence against being a dominant high-risk pathogenic mutation); and

- The documentation of non-quantitative methods that have been used to classify variants in the literature.

The qualitative classification criteria were validated againts a set of 170 assumed pathogenic variants (ie, nonsense, frameshift, splicing). Once their robustness was established, the scheme was first tested on a subset of 117 MMR gene variants with discordant classifications, and the criteria evolved and were refined by consensus to accommo­date new data and inconsistencies over multiple classification telecon­ferences and face-to-face meetings. By the end of 2013, the criteria were then applied retrospectively and to all remaining unique variants listed in the data­base, for a total of 2,370 variants4. The same procedure is continuing after the initial evaluation.

At the close of each VIC teleconference or meeting, consensus clas­sifications are noted. Where necessary, action items to improve or clarify classification include (i) calls for missing clinical and func­tional information for specific variants to committee members and the general InSiGHT membership; (ii) requests for more detailed data or data clarification from the authors of original publications; and (iii) reassessment of classification after additional data are obtained. At the end of the process, the InSiGHT database is updated with the final consensus classifications and the sup­porting data to ensure transparency.

1Plon, S.E. et al. Hum Mutat29, 1282–1291(2008).

2Arnold, S. et al. Hum Mutat 30, 757-70 (2009).

3Spurdle, A.B., et al. Hum Mutat 29, 1304-13 (2008).

4Thompson, BA, et al. Nat Genet. 46:107-115 (2014).

**Genes currently under review**: *MSH2, MLH1, PMS2, MSH6.*

**Future plans**: InSiGHT plans to expand its classification effort on other GI cancer predisposing genes, namely *APC* and *MUTYH*.

1. **Please list relevant publication(s) including PMID/PMCID which describe the variant classification process in detail and/or a publically accessible website which provides this information for the ClinGen Executive Committee and individuals using ClinVar.**

- Thompson BA, Spurdle AB, Plazzer JP, Greenblatt MS, Akagi K, Al-Mulla F, Bapat B, Bernstein I, Capellá G, den Dunnen JT, du Sart D, Fabre A, Farrell MP, Farrington SM, Frayling IM, Frebourg T, Goldgar DE, Heinen CD, Holinski-Feder E, Kohonen-Corish M, Robinson KL, Leung SY, Martins A, Moller P, Morak M, Nystrom M, Peltomaki P, Pineda M, Qi M, Ramesar R, Rasmussen LJ, Royer-Pokora B, Scott RJ, Sijmons R, Tavtigian SV, Tops CM, Weber T, Wijnen J, Woods MO, Macrae F, Genuardi M. Application of a five-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants lodged on the InSiGHT locus-specific database. Nat Genet. 46:107-115 (2014).

- http://insight-group.org/variants/classifications/