



Animal Genetic Testing Standardization (AGTS)

Organised by a Standing Committee: NO

Second meeting of workshop – vote needed at 2025 business meeting to establish as official ISAG standing workshop. Vote – was approved at Business Meeting.

Meeting information:

Date: 24 July 2025, Thursday

Time: 13:30 – 18:00 **Room:** 105 & 106

Number of participants: ~60

Chair:

Name: Leslie A. Lyons, PhD

Affiliation: University of Missouri

Contact email: lyonsla@missouri.edu

Agenda

- Review focus of the committee & working groups
- Introduce Steve Harrison – Ambry Genetics & ClinGen
- Present current status of efforts (Presentations: Leslie Lyons & Bart Broeckx)
- Establish goals for ISAG 2027
- Establish leadership for committee / working groups

Goals and Focus of AGTS

The AGTS committee will develop objectives, working groups and actionable items to develop criteria and assist the translation and interpretation of genetic testing methods, results, and reports, for geneticists, veterinarians, and animal breeders and owners.

- Four working groups have been developed to address genetic testing standardization.
- Each working group will include ISAG members representing all appropriate species.
- The working groups may seek information and support from non-ISAG groups, including OMIA, veterinary associations (WSAVA), animal registries, breeders, and other appropriate stakeholders.
- The working groups are expected to work towards publications of the standards developed.



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Four AGTS Working Groups

1) Nomenclature Working Group Focus, Accomplishments, Goal

Assign the gene / allele names for disease & phenotypic variants following current genetic standards

Presentation by Leslie A. Lyons, PhD, University of Missouri

Define criteria standards that may be required for a given species

Acronyms for cat breed names (consider Vertebrate Breed Ontology, cat fancy EMS codes....Mostly will follow cat fancy 3 letter EMS codes.

Define a random bred cat (RBC) - agreed

Select acronym for breeds in development – to be done by committee, accepted by cat breed organizations Fife & WCF (August/September 2025).

Fca126 positions for all cat variants - completed

Define allele names for phenotypes in cats – completed in workshop

Define allele names for disease reporting in cats - completed in workshop

Goal 2027 – continue similar effort for the horse, publish in BioRIV for ISAG review and support

Q&A:

- Q: How do we call a random bred cat?
A: Random bred (RBC) = cat on the street. (OMIA will change it after passing it through VBO)
- Q: How will we name gene regions?
A: OMIA-variant, Gene, cDNA Position, important to add reference genome.
- Q: Do we want the g. position, c. position or p.?
A: The idea is to use OMIA as a reference source instead of using the c., g. or p. position.
- Q: is it a good idea to add the original breed the variant was found in?
General answer: It might not be a good idea because the variant, whether it is in one or another breed, is disease causing. Conversely, this notation indicates more clearly what breed the variant was validated in originally and would give some indication of other breeds at risk – such as those of a breed family, or derived lineages.

2) Variant Pathogenicity Working Group Focus, Accomplishments, Goal

Assign classes of pathogenicity to animal variants following criteria established by the working group and where applicable, following standards set in research communities for human variants.

See recent publications:

Boeykens F, Abitbol M, Anderson H, Casselman I, de Citres CD, Hayward JJ, Häggström J, Kittleson MD, Lepri E, Ljungvall I, Longeri M, Lyons LA, Ohlsson Å, Peelman L, Smets P, Vezzosi T, van Steenbeek FG, Broeckx BJG. Development and validation of animal variant classification guidelines to objectively evaluate genetic variant pathogenicity in domestic animals. *Front Vet Sci.* 2024 Dec 5;11:1497817. doi: 10.3389/fvets.2024.1497817. PMID: 39703406; PMCID: PMC11656590.

Boeykens F, Abitbol M, Anderson H, Dargar T, Ferrari P, Fox PR, Hayward JJ, Häggström J, Davison S, Kittleson MD, van Steenbeek F, Ljungvall I, Lyons LA, Longeri M, Ohlsson Å, Peelman L, Dufaure de Citres C, Smets P, Turba ME, Broeckx BJG. Classification of feline hypertrophic cardiomyopathy-associated gene variants according to the American College of Medical Genetics and Genomics guidelines. *Front Vet Sci.* 2024 Feb 2;11:1327081. doi: 10.3389/fvets.2024.1327081. Erratum in: *Front Vet Sci.* 2024 Aug 12;11:1458433. doi: 10.3389/fvets.2024.1458433. PMID: 38371598; PMCID: PMC10873919.

Presentation by Bart Broeckx (University of Ghent) on his team's productivity and goals

Agreement on decision whether a variant falls in the scope, defined as “*The scope are single-gene disorders. These are disorders characterized by variants in a single gene with a high impact on disease risk, i.e. the impact of one variant is sufficient to cause disease (but does not have to cause disease in every individual due to e.g. reduced penetrance)*”: 93% interobserver agreement

Established criteria show high consistency amongst reviews and with published data, some variants need more detailed discussion. In more detail:

65% exact agreement amongst reviewers (median ACMG: 54%)

83% clinically important agreement amongst reviewers (median ACMG: 95%)

To increase agreement, tabulation errors should be avoided. Automated label suggestion can be helpful (*Excel file that allows this, has been created in the meantime*)

Some minor changes to criteria may be required and may need species specificity

Will share current manuscript with current effort in cats, dogs, horses with ISAG community for support

Intermediate goal (end of 2025): submit paper on reproducibility (results mentioned above) – discuss changes to criteria

Goal 2027 – Current work published and move forward with additional variants and species; consider new update of guidelines and, if improvements are suggested, present and discuss at ISAG 2027

Q&A

- Q: What if a label is inconsistent when assigned by three reviewers?
Suggested Approach: Prioritize variants with clinically significant disagreements.



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A: There is general agreement to follow this approach, provided that all variants will eventually be reviewed.

Remarks: A discussion on the timeline and criteria for completing the full review is needed as soon as possible.

Q: How should we reach a decision during discussions when there is no unanimous agreement: by majority vote, most commonly chosen label, or withholding a label?

A: The approach will be determined case by case.

Remarks: Expert opinion should carry more weight when present.

In some cases, it may be appropriate to withhold a label and instead indicate that further research is needed (e.g., classify as VUS – Variant of Uncertain Significance).

Individuals with a conflict of interest should not be voting.

Q: Where should newly labelled variants be made public, and can we use the phrase “ISAG endorsed”?

Remarks: Newly labeled variants will be made public on OMIA. While there is general support for this approach, there are concerns about using the term “endorsed”, which is considered too strong without approval from higher authorities.

General Agreement: Remove the phrase “ISAG endorsed” and retain the asterisk notation with an explanatory note at the bottom.

Q: Should we include the fulfilled/rejected criteria for each label individually?

Remarks: Adding this information per label would require significant effort from OMIA. A more efficient approach might be to link each label from OMIA to a central reference table. However, this would require funding to build a secure database to safeguard the data in case of system failures.

Answer: The general consensus is to link the labels on OMIA entries to a central table, with the goal of professionalizing and expanding the system in the future.

Q: Should variant classifications be published within the paper itself, or only on platforms like OMIA?

Answer: Following the approach used in human ACMG guidelines, it's preferable to link the classifications in the publication to a table in supplementary material as well as hosted on OMIA. This allows for greater flexibility to update classifications over time, while the publication can state that it reflects the most current version available at the time of writing.

Q: What is used to classify the variants?

A: Any publication can be used but should be referenced.

3) Comparison Testing Support & Data Sharing Working Group Focus, Accomplishments and Goals



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Task force to improve logistics of CT? Forensics has suggested multiple distribution points.

Assist with common issues across CTs – need consistent and well-defined instructions to be used by all CTs where applicable (Forensics required different approach)

Data sharing dbase considerations (Genoex, shariant, other) – need to explore, can this be combined with EU effort to register cats and dogs as part of reduction of imports and welfare concerns

What to do when labs outsource testing? How should this be reported and scored by ISAG?

Help select variants that should be part of a CT for a given species – difficult variants, common variants

Formats for genetic test reporting were presented and discussed. Ongoing discussion to continue by the working group.

Goal 2027 – meet more regularly with CT committees and have standard formats for next CT. Start CTs earlier?

4) Genetic Test Reporting Working Group Focus, Accomplishments and Goals

Formats for genetic test reporting were presented and discussed. Ongoing discussion to continue by the working group.

Working with WSAVA and other veterinary groups as well as other sub-committees to recommend specific tests for specific populations. Perhaps assist with counselling recommendations.

Develop consistent reporting schemes and verbiage (English, which could be translated into home language).

- Which tests should be offered?
 - Test/report rare diseases identified in only random bred cats?
- What is the advice to a breed(er) when a variant is identified in a new breed, but of only one or a few individuals?
 - Should lab be expected to confirm these findings by variant validation using another technique, ideally Sanger sequencing?
 - Should OMIA list these findings?

Goals 2027 – make some draft recommendations for the cat as based on work of the other committees.

Summary of the meeting:

Attendees were enthusiastic to continue the committee. Approximately 23 members of 60 attendees were assigned to working groups. Working group membership can be re-evaluated every 2 years to maintain or acquire needed expertise for goals, **non-ISAG**



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members can be included. Publications (nomenclature & pathogenicity) will be distributed for comment by ISAG members (via BioRxiv) to extend acceptance to a broader part of the ISAG membership

Votes:

Goals and Focus of AGTS (Voted - approved by attendees)

Four Working Groups Goals & Membership (Voted - approved by attendees)

New Committee chair – 1st official year

Chair: Leslie A. Lyons, PhD

Term of service 1st term: 2025 - 2029

Affiliation: University of Missouri

E-mail address: lyonsla@missouri.edu

AGTS Committee members

Other committee members	First term of service (from year to year)	Second term	Email address
Imke Tammen (OMIA)	2025 - 2029	N/A	Imke.tammen@sydney.edu.au
Bart Broeckx	2025 – 2029	N/A	Bart.broeckx@ugent.be
Tosso Leeb	2025 – 2029	N/A	tosso.leeb@unibe.ch
Jerold Bell	2025 – 2029	N/A	Jerold.Bell@tufts.edu
Robert Grahn	2025 – 2029	N/A	ragrahn@ucdavis.edu
Jessica Petersen	2025 – 2029	N/A	jessica.petersen@unl.edu
Steven Harrison	2025 – 2029	N/A	sharrison@ambrygen.com

**Working groups are open to participants, interested parties from ISAG 2023 also included

Nomenclature Working Group members (Dr. Lyons has an extended committee including cat breeders for cat work)

Other committee members	First term of service (from year to year)	Second term of service (from year to year)	Email address
Leslie A. Lyons	2025 - 2029	N/A	lyonsla@missouri.edu
Imke Tammen	2025 - 2029	N/A	Imke.tammen@sydney.edu.au
Ryan Ferretti	2025 - 2029	N/A	RFerretti@neogen.com
Robin Everts	2025 - 2029	N/A	reverts@etalondx.com
George Sofronidis	2025 - 2029	N/A	george@orivet.com
Jason Reding	2025 - 2029	N/A	Jason@studbook.co.za
Fabiana Michelsen de Andrade	2025 - 2029	N/A	fabiana.michelsen@hotmail.com



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Animal Variant Pathogenicity members (Dr. Broeckx has an extended committee)

Other committee members	First term of service (from year to year)	Second term of service (from year to year)	Email address
Bart Broeckx	2025-2029	N/A	Bart.broeckx@ugent.be
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Genetic Test Reporting working group members

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Peter Owolabi	2025-2029	N/A	opeterayo246@gmail.com
Rebecca Bellone	2025-2029	N/A	Rebecca R Bellone <rbellone@ucdavis.edu>
Jennifer Grahn	2025-2029	N/A	jcgrahn@ucdavis.edu

Comparison test support and data sharing working group members

Other committee members	First term of service (from year to year)	Second term	Email address
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Imke Tammen	2025-2029	N/A	Imke.tammen@sydney.edu.au
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Comparison test NO

Signature

Chair Leslie A. Lyons