All in the Name: A Review of Current Standards and the Evolution of Histopathological Nomenclature for Laboratory Animals

Susan A. Elmore, Robert Cardiff, Mark F. Cesta, Georgios V. Gkoutos, Edward Helton, Robert Hoehndorf, Charlotte M. Keenan, Colin McKerlie, Paul N. Schofield, John P. Sundberg and Jerrold M. Ward

Susan A. Elmore, MS, DVM, DCVP, DABT, FIATP, is an NTP Pathologist and Staff Scientist at the National Toxicology Program, National Institute of Environmental Health Sciences in the Research Triangle Park, North Carolina, USA.

Robert D. Cardiff, MD, PhD, is a Distinguished Professor of Pathology, Emeritus at the UCD Center for Comparative Medicine, University of California, and the Department of Pathology and Laboratory Medicine, School of Medicine, Davis, Davis California, USA.

Mark F. Cesta, DVM, PhD, DACVP, is an NTP Pathologist and Staff Scientist, leading the effort for establishment of the online NTP Nonneoplastic Lesion Atlas at the National Toxicology Program, National Institute of Environmental Health Sciences in the Research Triangle Park, North Carolina, USA.

Georgios V. Gkoutos, PhD, DIC, is the Professor of Clinical Bioinformatics, College of Medical and Dental Sciences, Institute of Cancer and Genomic Sciences Centre for Computational Biology, University of Birmingham in Birmingham, United Kingdom.

Edward Helton, PhD, is co-chair for the National Cancer Informatics Program's Imaging Informatics WG for cross NCI informatics at the Center for Bioinformatics and Information Technology's Clinical and Translational Informatics Section, National Cancer Institute in Rockville, MD, USA.

Robert Hoehndorf, PhD, is an Assistant Professor in Computer Science at the Computer, Electrical and Mathematical Sciences and Engineering Division, Computational Bioscience Research Center, King Abdullah University of Science and Technology in Thuwal, Kingdom of Saudi Arabia.

Charlotte M. Keenan, VMD, DACVP, is a Principle Consultant at C.M. ToxPath Consulting in Doylestown, Pennsylvania, USA and leads the international STP effort for the publication of the harmonization of nomenclature and diagnostic criteria (INHAND) in toxicologic pathology.

Colin McKerlie, DVM, DVSc, MRCVS, is a Senior Associate Scientist in the Translational Medicine Research Program at The Hospital for Sick Children and a Professor in the Department of Pathobiology & Laboratory Medicine in the Faculty of Medicine at the University of Toronto, Toronto, Ontario, Canada.

Paul N. Schofield, MA DPhil, is the University Reader in Biomedical Informatics, Department of Physiology, Development & Neuroscience, University of Cambridge, UK and is also an Adjunct Professor at The Jackson Laboratory, Bar Harbor, Maine, USA.

John P. Sundberg, DVM, PhD, DACVP, is a Professor at The Jackson Laboratory, Bar Harbor, Maine, USA

Jerrold M. Ward, DVM, PhD, DACVP, FIATP, is a Special Volunteer at the National Cancer Institute, National Institutes of Health, Bethesda, MD and is also Adjunct Faculty at The Jackson Laboratory, Bar Harbor, Maine.

Address correspondence to Dr. Susan A. Elmore, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27707 or email elmore@niehs.nih.gov.

Abstract

The need for international collaboration in rodent pathology has evolved since the 1970s, and was initially driven by the new field of toxicologic pathology. First initiated by the World Health Organization's International Agency for Research on Cancer for rodents, it has evolved to include pathology of the major species (rats, mice, guinea pigs, nonhuman primates, pigs, dogs, fish, rabbits) used in medical research, safety assessment and mouse pathology. The collaborative effort today is driven by the needs of the regulatory agencies in multiple countries, and by needs of research involving genetically engineered animals, for "basic" research, and for more translational preclinical models of human disease. These efforts led to the establishment of an international rodent pathology nomenclature program. Since that time, multiple collaborations for standardization of laboratory animal pathology nomenclature and diagnostic criteria have been developed, and just a few are described herein. Recently, approaches to a nomenclature that is amenable to sophisticated computation have been made available and implemented for large-scale programs in functional genomics and ageing. Most terminologies continue to evolve as the science of human and veterinary pathology continues to develop, but standardization and successful implementation remain as critical for scientific communication, now as ever in the history of veterinary nosology.

Keywords

International Agency for Research on Cancer; International Harmonization of Nomenclature and Diagnostic Criteria; International Mouse Phenotyping Consortium; Mouse Pathology Ontology; National Cancer Institute Mouse Models of Human Cancer Consortium; National Toxicology

Program Nonneoplastic Lesion Atlas; Nomenclature; Standard for Exchange of Nonclinical Data.

History of International Laboratory Animal Pathology Nomenclature

The use of any standardized nomenclature for rodent pathology perhaps began in the 1970s with the publication of a series of tumor pathology books (on mice, rats and hamsters) by the International Agency for Research in Cancer (IARC), World Health Organization (WHO), Lyon, France. Dr. Vladimir Turusov, a medical pathologist, was the initial editor of a book series and chapter authors were invited from Europe, Japan and the USA (Turusov 1973, 1980, 1983, 1990, 1994). In the 1990s, Ulrich Mohr was editor for the second and third IARC series on rats and mice (Mohr 1997, 2001). In these series, international committees of pathologists prepared monographs on tumors of each organ system for rats and one book for mice. In the early 1990s, committees for nomenclature of tumors and non-proliferative lesions for each organ system of rats and mice were established as Guides for Toxicologic Pathology, a system of standardized nomenclature and diagnostic criteria (SNNDC), by a collaboration of the Armed Forces Institute of Pathology (AFIP), American Registry of Pathology (ARP) and the Society of Toxicologic Pathology (STP). The first published series was on rat pathology and was published by the AFIP and are presently online (https://toxpath.org/ssndc.asp). From 1983 to1996, The International Life Sciences Institute sponsored a series of thirteen Monographs on Pathology of Laboratory Animals led by T. C. Jones, U. Mohr and R. D. Hunt (Jones et al; https://link.springer.com/bookseries/780). During the same period, the National Toxicology Program (NTP) staff pathologists, contractors and collaborators published 2 books on rat and mouse pathology (Boorman et al. 1990; Maronpot 1999). These efforts led to the establishment of an international rodent pathology nomenclature program (International Harmonization of Nomenclature and Diagnostic Criteria – INHAND) involving several of the national societies of toxicologic pathology.

International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) for use in Toxicology Safety Assessment

In 2005, the Strategic and Regulatory Policy Committee (SRPC) of the STP determined that there was need for a revision of the earlier Standardized System of Nomenclature and Diagnostic Criteria (SSNDC) guides. The European Society of Toxicologic Pathology (ESTP), in conjunction with the Registry of Industrial Toxicology Animal-data (RITA), endorsed the proposal in late 2005. In 2006, the Japanese Society of Toxicologic Pathology (JSTP) and the British Society of Toxicologic Pathology (BSTP) joined the initiative, providing a truly global participation. Members of these major Societies of Toxicologic Pathology (JSTP, BSTP, ESTP and STP) and RITA are now engaged in an international collaborative effort (INHAND) to codify and publish uniform nomenclature for both proliferative and non-proliferative lesions in laboratory rodents. Several features unique to this effort include: 1) a truly international scope, 2) implementation of an open comment period allowing a wide group of toxicologic pathologists the opportunity to provide input, 3) inclusion of neoplastic and nonneoplastic terminology, and 4) availability in a web-based format along with publication in society journals. Project oversight is provided by the Global Editorial and Steering Committee (GESC) which consists of members from each of the major Societies of Toxicologic Pathology (Figure 1). Each rodent organ system or non-rodent species organ working group consists of a chairperson and members from each of the major societies of toxicologic pathology, drawing upon a diversity of experience and background with individuals from industry, academia, and government.

The Rodent Organ Working Groups (?) (OWGs) have the responsibility to prepare the nomenclature guidelines for both proliferative and non-proliferative lesions of rats and mice for their assigned organ system – 15 total systems. The Non-rodent Species Working Groups

(NRWGs) cover terminology specific to a species as well as noting diagnostic criteria that may be different from rodents for common lesions. The NRWGs include non-human primate, dog, minipig, rabbit and fish. In addition to lesions which occur spontaneously, the groups are asked to determine if there are common, xenobiotic-induced lesions for which standardized nomenclature might be needed. The working groups draw heavily from existing nomenclature documents, websites, and publications including prior work of the RITA and the SSNDC. For each diagnostic entity, the working groups select a preferred diagnosis and acceptable alternative diagnoses, provide diagnostic criteria and differential diagnosis, prepare representative photomicrographs, and also provide a comment section with key references. In general, working groups develop nomenclature that is primarily descriptive in nature and denote findings which can be documented from the review of routine histologic specimens. Incorporating specific diagnostic entities such as an infectious disease or that imply a process that cannot be ascertained from routine histologic specimens (e.g., phospholipidosis) is generally not recommended.

Finalized nomenclature is available to toxicologic pathologists, and the broader scientific community, in both electronic and print forms. The print-based publications are available in the toxicologic pathology journals: *Toxicologic Pathology,* the official journal of STP, BSTP and ESTP (http://journals.sagepub.com/home/tpx) and the *Journal of Toxicologic Pathology* which is the official journal of JSTP (https://www.jstage.jst.go.jp/browse/tox). Electronic access is via the global open Registry Nomenclature Information System (goRENI) website (https://www.goreni.org) or the journal websites (https://www.toxpath.org/inhand.asp#pubg or https://www.jstage.jst.go.jp/browse/tox).

Substantial progress has been made to date – 12 of the 15 rodent organ systems have been published: Respiratory System (Renne et al. 2009), Hepatobiliary System (Thoolen et al.

2010), Urinary System (Frazier et al. 2012), Nervous System (Kaufmann et al. 2012), Mammary, Zymbal's, Preputial and Clitoral Glands (Rudmann et al. 2012), Male Reproductive System (Creasy et al. 2012), Soft Tissue (Greaves et al. 2013), Integument (Mecklenburg et al. 2013), Female Reproductive System (Dixon et al. 2014), Digestive System (Nolte et al. 2016), Cardiovascular System (Berridge et al. 2016), and Skeletal System and Tooth (Fossey et al. 2016). To address consistent terminology for cell death, Recommendations from an Apoptosis/Necrosis Working Group was published by Elmore et al. in 2016. The Endocrine and Special Senses Systems and the Hematopoietic and Lymphoid System are scheduled for publication in 2018/2019.

An important aspect of the INHAND project is utilization of goRENI. ESTP offered access to an open version of goRENI to serve as a platform. Access to goRENI is restricted to members of the participating STPs (Vahle et al. 2006; Mann et al. 2012). Once access is granted, pathologists can navigate by organ systems and select a diagnosis they would like to view. Within the goRENI system, each diagnostic entity is referred to as a manuscript. An example is provided in Figure 2 of the written information and photographic illustrations provided for a kidney oncocytoma.

Although the published INHAND nomenclature for each organ system is expected to be very comprehensive, it is recognized that additional lesions may need to be included, inaccuracies corrected as they become apparent, or changes to terminology made based on new scientific information. To address this, a formal change control process was implemented in 2013 and is available on www.goreni.org and each pathology Society website. Society members are encouraged to submit recommendations for changes to the nomenclature systems and provide

justifications for such changes through this mechanism. Updates will be posted on goRENI, and this will be the source for the most current information.

The GESC and STP, BSTP, ESTP, and JSTP leadership recognize the significant efforts of all of those serving on the rodent OWGs and NRWGs, and look forward to working with the global toxicologic pathology community as additional systems are drafted, reviewed, and completed. The international scope and review of the INHAND documents will provide a strong framework for use by pathologists and regulatory agencies that are engaged in the safety assessment of drugs, biologics, and chemicals.

Standard for Exchange of Nonclinical Data (SEND)

SEND is a standardized procedure for submitting data from nonclinical studies to the Food and Drug Administration (FDA) electronically and in a standardized format (Keenan and Goodman 2014). During 2011, INHAND GESC representatives attended meetings with representatives of the FDA Center for Drug Evaluation and Research (CDER), Clinical Data Interchange Standards Consortium (CDISC), and the National Cancer Institute (NCI) Enterprise Vocabulary Services (EVS) to initiate integration of INHAND terminology as the preferred terminology for SEND. INHAND GESC representatives work with the SEND Controlled Terminology (CT) committee to provide definitions for base processes and modifiers associated with the INHAND published terminology. Any issues or questions are presented to the full GESC and/or appropriate INHAND Working Group for resolution. The initial list for the SEND codelist of nonneoplastic (NONNEO) microscopic pathology contains terms from published INHAND organ systems. The list will continue to grow as INHAND publishes additional organ systems. Some terms on the NONNEO codelist may look different from how they have been

presented in the INHAND publications. Terms on the NONNEO codelist are mostly generic and can be used across tissues, where appropriate. INHAND published terms have been modified to fit the SEND standard in some cases by being broken into base process and modifiers. For example, the INHAND term Necrosis, zonal would be separated into NECROSIS for population in MISTRESC (Microscopic Standardized Result) and ZONAL in MIDISTR (Microscopic Distribution). Tissue specific terms from INHAND are included on the NONNEO codelist when it is important to use the exact term representing a spectrum of tissue changes (example – focus of cellular alteration). In the process of mapping terms from INHAND to SEND, some inconsistencies have been noted for the same term across several organ systems (example – thrombus vs thrombosis). These will be harmonized using the new change control process and the most current terminology will be available on the goRENI website. An example of a nomenclature map with INHAND terminology is shown in Figure 3. The most current SEND controlled terminology can be found at the NCI EVS site: https://evs.nci.nih.gov/ftp1/CDISC/SEND/.

National Toxicology Program (NTP) Nonneoplastic Lesion Atlas

Assessing the carcinogenicity of agents of concern in its rodent models has been at the core of the NTP's testing program; however, in recent years, the NTP has increased its focus on nonneoplastic lesions, many of which have been linked to occupational or environmental exposures. Diagnosing nonneoplastic lesions in toxicity studies presents a challenge in that there can be variation in terminology and diagnostic strategy. With nonneoplastic lesions, there are often several related lesions present concurrently, such as inflammation, necrosis or degeneration, fibrosis, and regeneration. Some pathologists record each lesion individually,

while others record the predominant lesion, or the primary process, and describe other lesions or features in the pathology narrative. Additionally, it can be difficult to determine which is the primary lesion, or which is the primary process. Also, the terminology used by different pathologists can vary based on training, experience, and personal opinion. In an effort to standardize the nomenclature and diagnostic strategy for NTP studies, the NTP created the Nonneoplastic Lesion Atlas (NNLA). The goal of the NNLA is to create a more consistent database of nonneoplastic lesions, which would allow comparison across studies, facilitate data mining, and allow for the generation of historical control data for some nonneoplastic lesions.

The NNLA is an online guide for the diagnosis and recording of nonneoplastic lesions in studies conducted by the NTP. It is organized by organ system and subdivided by tissue. Each page discusses a single lesion and provides recommendations for terminology and diagnostic strategy. The NNLA also provides references, links to related lesions, other useful information about the lesions, and thousands of zoomable photos of the lesions. The NTP has made every effort to be consistent with the terminology presented in the INHAND in Rats and Mice . The NNLA can be a valuable supplement to the INHAND documents.

Since the NNLA is an online document, it can (and will) be updated as the field of toxicologic pathology changes. It is searchable, downloadable, and available at https://ntp.niehs.nih.gov/nnl/. Though its main purpose is as a guide for toxicologic pathologists reading NTP studies, it is available free for public use around the world. It can be used by any toxicologic or pathology laboratory wanting to standardize their own database, by other scientists evaluating tissues, and by students as a training aid.

National Cancer Institute (NCI) Mouse Models of Human Cancer Consortium (MMHCC Nomenclature)

The advent of genetic engineering opened up a new era in animal research. Suddenly, the cell and molecular biologist could determine the effect of genetic mutations and selected engineered mutations in living mammalian organisms. Testing your mutation in a mouse fulfilled the "modern Koch's postulates". Rodents were once valued in cancer research because they spontaneously developed neoplasia in specific organs. In fact, they led the way to the understanding of oncogenic viruses. However, after investigators became equipped with an endless list of genes, they wished to know whether their gene(s) caused cancer in their favorite organ and whether or not their tumors resembled the comparable human tumor.

The NCI started exploring these questions by organizing and convening a Breast Cancer Consensus Meeting in Annapolis Maryland in 1999. The meeting included oncologists, modelers, breast pathologists and comparative or veterinary pathologists. The pathologists were tasked with developing a taxonomy and vocabulary that could be used to compare and contrast breast cancers in human and genetically engineered mice. The pathologists responded with a recommended taxonomy and a landmark paper (Cardiff et al. 2000).

With NCI's organization of the Mouse Models of Human Cancer Consortium groups, under the NCI Division of Cancer Biology's extramural grant program, each of nine organ systems were tasked with developing comparable (human and mouse) consensus pathology meetings. In preparation, the MMHCC met with the NCI vocabulary informatics experts to discuss the classification and nomenclature for each organ system. This exercise was accompanied by consensus meetings for each organ composed of committees of medical and veterinary pathologists, and PhD researchers from various medical and veterinary colleges,

government, and private research institutes. In some cases, the meetings were repeated with follow-up meetings. In some instances, specific subsets of issues, such as preneoplasia, were addressed (Cardiff et al. 2006).

The strength of the resulting nomenclatures was that the similarities and differences in the anatomy, physiology, and pathology of diseases were compared and contrasted by experts and the information became generally available. While instances of similarities in tumor histopathology between the two species have been recorded, the classifications generally lacked the granularity needed to satisfy the investigators. The MMHCC classification was merged with the NCI vocabularies and no longer exists as an independent taxonomy. The results of each pathology committee group were published in refereed journals (Boivin et al. 2003; Hruban et al. 2006; Ittmann et al. 2013; Kogan et al. 2002; Morse et al. 2002; Nikitin et al. 2004; Shappell et al. 2004; Stemmer-Rachamimov et al. 2004; Washington et al. 2013; Weiss et al. 2002). These publications report the comparative pathology for organ specific carcinogenesis for the purpose of developing mouse models of cancer.

Computable Terminology: Development and Implementation of the Mouse Pathology Ontology (MPATH) for use in Mouse Research

MPATH is an online structured vocabulary of mutant and transgenic mouse pathological lesions and processes (http://bioportal.bioontology.org/ontologies/MPATH). The historical motivation for the generation of MPATH was a response to the initiation of a database project, funded by the European Commission, to produce a definitive image resource for rodent pathology called Pathbase (http://www.pathbase.net ; Schofield et al. 2004). The community tasked to develop this resource was drawn from experts in the fields of rodent toxicopathology

and human anatomic pathology. This grouping expanded considerably in number and specialty as the ontology grew (Schofield et al. 2010). At the time in which MPATH was developed (1999-2004) ontologies were being created and implemented for the Mouse Genome Informatics (MGI) and related databases covering the areas of gene function, phenotype (Smith et al. 2005b), and anatomy (Ringwald et al. 2001). It became clear in these and other areas that standard terminologies, computable using biosemantic techniques (Bodenreider et al. 2004; Lord et al. 2003; Smith et al. 2003) were highly desirable. The ontology that emerged from these efforts, MPATH, was manually created by pathologists over a period of a decade from 1999-2010 with the help of colleagues from across Europe, North America and Japan.

Recently MPATH was adopted for the computational capture of gross and microscopic anatomic pathology from the primary phenotyping program of the European Mouse Disease Clinic (EUMODIC) project (Ayadi et al. 2012) and subsequently the International Mouse Phenotyping Consortium's (IMPC) globally coordinated mutant strain production and phenotyping program, and implemented as the terminology in the Jackson Laboratory's Nathan Shock Aging Institute large scale mouse lifespan study (Sundberg et al. 2011; Sundberg et al. 2016; Yuan et al. 2009). For both projects, further development of the ontology was undertaken with changes in the structure of several areas and a large increase in the number of terms included, together with an expansion of the textual class definitions.

MPATH is constructed according to ontological "good practice" rules and is consistent with the Open Biological and Biomedical Ontology (OBO) Foundry principles (Smith et al. 2007). One criterion adopted from the OBO Foundry is the separation of physical pathological entities and pathological processes. Such a separation also facilitates automated reasoning across the ontology and integration and interoperability with OBO Foundry ontologies. MPATH

therefore consists of two major branches, one containing pathological processes and another containing pathological structures. Each branch is itself constructed as a taxonomy of classes linked by logical axioms, or relations (Smith et al. 2005a). The majority of axioms in MPATH are subclass (or 'is-a') relations, asserting that a given class is a subclass of a parental class eg. choriocarcinoma '*is-a'* carcinoma. These axioms allow computational work to be done with the data, bridging between different groups and expand how searches are done. The hierarchical organization of MPATH will be familiar to anyone with experience of taxonomies, and the branches within are derived from traditional histopathological classifications of lesions and processes. MPATH does not contain classes representing a "disease", which often include many lesions and have distinct etiological origins; this type of entity is more usefully captured with a disease ontology such as the Human Disease Ontology (DO) as described by Kibbe et al. 2015 (http://www.disease-ontology.org). There are strong arguments, mainly from experience in toxicologic pathology, that a descriptive (anatomic) coding rather than diagnostic is the most useful way to code and analyze pathology-based observations and in fact MPATH can be used in the computational definitions of higher order disease classes from other ontologies such as the DO.

MPATH currently has 888 classes in a hierarchy nine layers deep that may be obtained from its repository (https://raw.githubusercontent.com/PaulNSchofield/mpath/master/mpath.obo). Currently, over 90% of the classes have textual definitions. The ontology was specifically designed for use by trained histopathologists. However, MPATH has the additional advantage to permit computation and is amenable to machine presentation in data capture software (Sundberg et al. 2009).

Within a single hierarchy it is not feasible to capture, in a precomposed way, a class for every type of lesion of every subtype and stage, for every tissue in which it occurs. This would give rise to ontology "bloat" and it becomes very difficult to handle for humans and computers alike. To solve this problem, we have included some of the more common precomposed classes in MPATH; for example, the names of many neoplasms contain anatomic information such as brochioloalveolar adenocarcinoma. For cases where such a precomposed term is not available, users are able to use a postcomposition approach. In the postcomposition of ontology classes different elements of the description are taken from different ontologies and used to create a formal computational statement to describe an observation. In the case of MPATH, classes may be combined with those from the mouse adult anatomy ontology (MA; https://bioportal.bioontology.org/ontologies/MA), to described the location of the lesion; they may then be further qualified with one or more classes that characterize qualities, from the Phenotype and Trait Ontology (PATO; http://agroportal.lirmm.fr/ontologies/PATO) (Gkoutos et al. 2017). PATO is an ontology of qualities that qualify or provide formal attributes to an entity or a process, such as color, texture, or more complex qualities such as malignancy (Gkoutos et al. 2005). The PATO subset derived for use for histopathology can be found as a "slim" in the main PATO file available on from the code repository (https://raw.githubusercontent.com/pato-ontology/pato/master/pato.obo). An example of a postcomposed term using PATO, MA, and MPATH is shown in Figure 4.

The computational advantages of using ontologies for terminological coding are very significant. At the simplest level the subclass relations provided by the hierarchy allows for query expansion and for coding of a less specific parent term when there is some doubt as to which term is appropriate. The use of standardized terms – the class labels – allows the ontology

to be used for text mining (Hoehndorf et al. 2015) and greatly facilitates the process of coding. However, the more important advantages lie in the ability to classify, combine and split lesions for analysis. When a large experiment is coded using MPATH (and other ontologies such as MA) it becomes possible to quantify the occurrence of specific cancers, as well as all cancers, and cancer types automatically, without having to recode or manually recalculate the primary coding. Similarly it is possible to compute overrepresentation of particular lesions (Hoehndorf et al. 2016), types of lesions or anatomical location of lesions in one group of animals versus another. We can use MPATH to precisely calculate the similarity in disease profiles between two animals or groups of animals using semantic similarity measures. Furthermore, it becomes possible to combine and semantically integrate different datasets that use MPATH for coding pathology even if the investigators worked at different levels of granularity or different geographic locations.

Experience of coding a study using MPATH and MA has been very positive. In a large-scale aging study, conducted on 28 inbred strains, the type and diversity of spontaneous diseases that aging mice develop were captured using the Mouse Disease Information System (MoDIS) system (Sundberg et al. 2011; Sundberg et al. 2016). In addition to MA and MPATH, the terminologies in MoDIS were designed to be extended to take user-defined diagnostic terms, such as pseudoxanthoma elasticans (PXE), to allow targeted searches to be done on specific disease entities (Sundberg et al. 2009; Sundberg et al. 2010; Sundberg et al. 2008). A total of 20,885 different diagnoses were made by the same pathologist from reading approximately 50,000 slides from 2,000 individual mice, with an average of 12 diagnoses per mouse in the study. This data has already been successfully utilized for a series of genome-wide association (GWA) and other studies (Berndt et al. 2014; Berndt et al. 2016; Li et al. 2016). Work in

progress is generating a comprehensive quantitative survey of disease frequency across the lifespan of these strains.

Standardized Histopathology Terminology Implemented by the International Mouse Phenotyping Consortium (IMPC)

The IMPC was established in 2011 as a global consortium of large-scale mouse production and phenotyping centers (Brown and Moore 2012). It consists of 19 research institutions and 5 national funders from 11 countries (http://www.mousephenotype.org/data/documentation/aboutImpc#howdoesimpcwork). The Consortium's ten-year goal is to generate a 'knockout' mutant for every protein coding gene in the mouse genome in an effort to characterize the phenotype(s) that each gene confers. All mutant strains as live mice (if available) or cryopreserved sperm and phenotype data are freely available to the public, including summary data for a cohort compared with multiple wildtype controls. To overcome any potential issue of publication bias, the IMPC's phenotype data includes all negative results as well as positive findings and an automated statistical analysis tool (Kurbatova et al. 2015) is used to ensure the validity of the post quality-controlled data made available to the research community. The IMPC's web portal (http://www.mousephenotype.org) provides a unified single point of access to the production and phenotyping data and enables researchers to formulate hypotheses for biomedical and translational research as well as purpose-driven preclinical studies. In the past five years, data for more than 4,000 genes have been captured by 10 IMPC centers around the world.

The IMPC's standardized phenotyping pipeline has been carefully designed, validated, and implemented at each participating center. An *International Mouse Phenotyping Resource of Standardised Screens* (IMPReSS) protocol including procedure, data type description, and metadata are available for every test through the IMPC's portal (http://www.impc.org/impress). Cohorts of at least 7 female and 7 male adult mutants from each strain enter the pipeline at 4 weeks of age. Then a sequential set of clinical phenotyping tests to assay all major adult organ systems and most areas of major human disease is performed in order to identify abnormal phenotypes of functional, biological, or disease relevance. The majority of IMPC tests are mandatory in the pipeline; however several optional tests have been standardized to use by individual centers where specialized equipment and expertise is available. At 16 weeks of age, a standardized panel of terminal tests, including an optional histopathology test, is done to complete the pipeline (Adissu et al. 2014; https://www.mousephenotype.org/impress/protocol/276/7).

Similar to all of the clinical and terminal tests that the IMPC phenotyping pipeline uses, the histopathology test, and the data it generates, must be high-throughput, robust, and standardized to facilitate reliable and reproducible downstream analysis by the global research community (Mallon et al. 2012; Ring et al. 2015). Histopathology has always played a pivotal role in hypothesis-driven studies, purpose-driven translational investigations, and preclinical assessment of mouse models, providing important insight into the morphological (structural) consequences and mechanisms of gene function or dysfunction and therapeutic effect and safety. In the context of the IMPC's high-throughput phenotyping pipeline, the histopathology test's objectives using a panel of tissues (25 required for female mice; 26 required for male mice) collected from 2 female and 2 male mutant mice from each strain are to:

1) Identify abnormalities ('lesions') correlated with clinical phenotype (e.g. clinical ataxia, cerebellar histopathology).

2) Identify significant abnormalities not directly correlated with clinical phenotype, often the result of gene pleiotropy whereby a single mutate gene causes multi-system changes (e.g. clinical ataxia, liver histopathology).

3) Identify significant abnormalities that are novel findings in strains with no identified clinical phenotype.

4) Classify any of these findings as 'not significant' (interpreted by the histopathologist to be background-related or incidental) or 'significant' (interpreted by the histopathologist to not be a background-related finding; e.g., low-incidence retinal dysplasia) or incidental finding (e.g., focal hepatic microgranuloma).

To achieve the same objectives for histopathology data of standardization, quality-control, and semantic standards (i.e. machine-search ability by web portal users) required by the IMPC, the Consortium's Morphology Working Group has developed a histopathology ontology that is a compilation of three well-established ontologies described in other sections of this paper; MA, PATO, and MPATH. The data capture, annotation, and storage system developed at The Centre for Phenogenomics (TCP; http://www.phenogenomics.ca) in Toronto is provided as an example of integration, implementation, and use of the IMPC histopathology ontology within an IMPC center. Briefly, TCP histopathology data acquisition work flow supported by the system's user interface (Figure 5) and integration of MA, PATO, and MPATH ontologies within the database typically includes several steps:

1) Select a mouseID on the worklist for review.

2) The required tissue list is auto-populated.

3) Each individual tissue row includes the MA term name and term ID (e.g. liver [MA:00003581]) and entry fields with dropdown lists to select PATO descriptors (Severity, Duration, Distribution), MPATH Process Terms (e.g. inflammation [MPATH:212]), and MPATH Diagnosis (entity) Terms (e.g. granuloma [MPATH:847]).

4) Add Free Text Diagnostic Term if necessary, add Pathologist Comments if appropriate, and toggle the Significance Score check-box (i.e. unchecked equals Not Significant, checked equals Significant).

Note that certain Term fields are auto-populated for efficient workflow (if no findings to annotate, no entry effort required) and to comply with the minimum required dataset for successful upload to the IMPC Data Center. Additional functionality includes parsed dropdown lists (e.g., liver row's MPATH Process Terms and MPATH Diagnostic Terms only provide term options applicable to liver pathology) (Figure 6).

The IMPC histopathology ontology described here is fully integrated in the IMPC's central database. Therefore, any center in the Consortium that is doing histopathology at IMPReSS standards can upload data compliant with the standardization, quality-control, and machine-readable requirements of the IMPC. Using MA, PATO, and MPATH, each well established, publically available, and actively curated extant ontologies was, and is, essential to this process. Data display at the portal is in active development.

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References

1. Adissu HA, Estabel J, Sunter D, Tuck E, Hooks Y, Carragher DM, Clarke K, Karp NA, Wellcome Trust Sanger Institute SM, Newbigging S et al. 2014. Histopathology reveals correlative and unique phenotypes in a high throughput mouse phenotyping screen. Dis Model Mech. 7(5):515-24

2. Ayadi A, Birling MC, Bottomley J, Bussell J, Fuchs H, Fray M, Gailus-Durner V, Greenaway S, Houghton R, Karp N et al. . 2012. Mouse large-scale phenotyping initiatives: overview of the European Mouse Disease Clinic (EUMODIC) and of the Wellcome Trust Sanger Institute Mouse Genetics Project. Mamm Genome 23(9-10):600-10.
3. Berndt A, Ackert-Bicknell C, Silva KA, Kennedy VE, Sundberg BA, Cates JM, Schofield PN, Sundberg JP. 2016. Genetic determinants of fibro-osseous lesions in aged inbred mice. Exp Mol Pathol 100(1):92-100.
4. Berndt A, Sundberg BA, Silva KA, Kennedy VE, Richardson MA, Li Q, Bronson RT, Uitto J, Sundberg JP. 2014. Phenotypic characterization of the KK/HlJ inbred mouse strain. Vet Pathol 51(4):846-57.
5. Berridge BR, Mowat V, Nagai H, et al. Non-proliferative and Proliferative Lesions of the Cardiovascular System of the Rat and Mouse. J Toxicol Pathol. 2016;29(3 Suppl):1S-47S.
6. Bodenreider O, Smith B, Burgun A. 2004. The Ontology-Epistemology Divide: A Case Study in Medical Terminology. Form Ontol Inf Syst 2004:185-195.
7. Boivin GP, Washington K, Yang K, Ward JM, Pretlow TP, Russell R, et al. Pathology of mouse models of intestinal cancer: consensus report and recommendations. Gastroenterology. 2003;124(3):762-77.
8. Boorman GA, Eustis SL, Elwell MR, Montgomery CA, MacKenzie WF. 1990. Academic Press, Inc. San Diego, CA. 1-580.
9. Brown SD, Moore MW. 2012. Towards an encyclopaedia of mammalian gene function: the International Mouse Phenotyping Consortium. Dis Model Mech 5(3):289-92.

10. Cardiff RD, Anver MR, Boivin GP, Bosenberg MW, Maronpot RR, Molinolo AA, et al. Precancer in mice: animal models used to understand, prevent, and treat human precancers. Toxicol Pathol. 2006;34(6):699-707.
11. Cardiff RD, Anver MR, Gusterson BA, Hennighausen L, Jensen RA, Merino MJ, et al. The mammary pathology of genetically engineered mice: the consensus report and recommendations from the Annapolis meeting. Oncogene. 2000;19(8):968-88.
12. Creasy D, Bube A, de Rijk E, et al. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. Toxicol Pathol. 2012;40(6 Suppl):40S-121S.
13. Dixon D, Alison R, Bach U, et al. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. J Toxicol Pathol. 2014;27(3-4 Suppl):1S-107S.
14. Elmore SA, Dixon D, Hailey JR, et al. Recommendations from the INHAND Apoptosis/Necrosis Working Group. Toxicol Pathol. 2016;44(2):173-188.
15. Fossey S, Vahle J, Long P, Schelling S, Ernst H, Boyce RW, Jolette J, Bolon B, Bendele A, Rinke M et al. . 2016. Nonproliferative and Proliferative Lesions of the Rat and Mouse Skeletal Tissues (Bones, Joints, and Teeth). J Toxicol Pathol 29(3 Suppl):49S-103S.
16. Frazier KS, Seely JC, Hard GC, Betton G, Burnett R, Nakatsuji S, Nishikawa A, Durchfeld-Meyer B, Bube A. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. Toxicol Pathol 40(4 Suppl):14S-86S.
17. Gkoutos GV, Green EC, Mallon AM, Hancock JM, Davidson D. 2005. Using ontologies to describe mouse phenotypes. Genome Biol 6(1):R8.

18. Gkoutos GV, Schofield PN, Hoehndorf R. 2017. The anatomy of phenotype ontologies: principles, properties and applications. Brief Bioinform. Apr 6. doi: 10.1093/bib/bbx035. [Epub ahead of print]

19. Greaves P, Chouinard L, Ernst H, Mecklenburg L, Pruimboom-Brees IM, Rinke M, Rittinghausen S, Thibault S, Von Erichsen J, Yoshida T. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. J Toxicol Pathol 26(3 Suppl):1S-26S.

20. Hoehndorf R, Gkoutos GV, Schofield PN. 2016. Datamining with Ontologies. Methods Mol Biol 1415:385-97.

21. Hoehndorf R, Schofield PN, Gkoutos GV. 2015. Analysis of the human diseasome using phenotype similarity between common, genetic, and infectious diseases. Sci Rep 5:10888.

22. Hruban RH, Adsay NV, Albores-Saavedra J, Anver MR, Biankin AV, Boivin GP, et al. Pathology of genetically engineered mouse models of pancreatic exocrine cancer: consensus report and recommendations. Cancer Res. 2006;66(1):95-106.

23. Ittmann M, Huang J, Radaelli E, Martin P, Signoretti S, Sullivan R, et al. Animal models of human prostate cancer: the consensus report of the New York meeting of the Mouse Models of Human Cancers Consortium Prostate Pathology Committee. Cancer Res. 2013;73(9):2718-36.

24. Jones, TC, Mohr, U, Hunt RD. Monographs on Pathology of Laboratory Animals. Berlin: Springer-Verlag. 1983-1996. (volumes by organ system or species)

25. Kaufmann W, Bolon B, Bradley A, Butt M, Czasch S, Garman RH, George C, Gröters S, Krinke G, Little P et al. . 2012. Proliferative and nonproliferative lesions of the rat and mouse central and peripheral nervous systems. Toxicol Pathol 40(4 Suppl):87S-157S.
26. Keenan CM, Goodman DG. 2014. Regulatory Forum commentary: through the looking glass--SENDing the pathology data we have INHAND. Toxicol Pathol 42(5):807-10.
27. Kibbe WA, Arze C, Felix V, Mitraka E, Bolton E, Fu G, Mungall CJ, Binder JX, Malone J, Vasant D et al. . 2015. Disease Ontology 2015 update: an expanded and updated database of human diseases for linking biomedical knowledge through disease data. Nucleic Acids Res 43(Database issue):D1071-8.
28. Kogan SC, Ward JM, Anver MR, Berman JJ, Brayton C, Cardiff RD, et al. Bethesda proposals for classification of nonlymphoid hematopoietic neoplasms in mice. Blood. 2002;100(1):238-45.
29. Kurbatova N, Mason JC, Morgan H, Meehan TF, Karp NA. 2015. PhenStat: A Tool Kit for Standardized Analysis of High Throughput Phenotypic Data. PLoS One 10(7):e0131274.
30. Li Q, Berndt A, Sundberg BA, Silva KA, Kennedy VE, Cario CL, Richardson MA, Chase TH, Schofield PN, Uitto J et al. . 2016. Mouse genome-wide association study identifies polymorphisms on chromosomes 4, 11, and 15 for age-related cardiac fibrosis. Mamm Genome 27(5-6):179-90.
31. Lord PW, Stevens RD, Brass A, Goble CA. 2003. Semantic similarity measures as tools for exploring the gene ontology. Pac Symp Biocomput:601-12.

32. Mallon AM, Iyer V, Melvin D, Morgan H, Parkinson H, Brown SD, Flicek P, Skarnes WC. 2012. Accessing data from the International Mouse Phenotyping Consortium: state of the art and future plans. Mamm Genome 23(9-10):641-52.

33. Mann PC, Vahle J, Keenan CM, Baker JF, Bradley AE, Goodman DG, Harada T, Herbert R, Kaufmann W, Kellner R et al. 2012. International harmonization of toxicologic pathology nomenclature: an overview and review of basic principles. Toxicol Pathol 40(4 Suppl):7S-13S.

34. Maronpot RR, Boorman, GA, Baul BW. 1999. Pathology of the Mouse. Cache River Press, Vienna, Il. 1-699.

35. Mecklenburg L, Kusewitt D, Kolly C, Treumann S, Adams ET, Diegel K, Yamate J, Kaufmann W, Müller S, Danilenko D et al. . 2013. Proliferative and non-proliferative lesions of the rat and mouse integument. J Toxicol Pathol 26(3 Suppl):27S-57S.

36. Mohr, U (ed). International Classification of Rodent Tumours. Part I. The Rat. IARC Scientific Publications No. 122, 1997

37. Mohr, U (ed). International Classification of Rodent Tumours: The Mouse, Heidelberg: Springer-Verlag, pp 474, 2001

38. Morse HC, 3rd, Anver MR, Fredrickson TN, Haines DC, Harris AW, Harris NL, et al. Bethesda proposals for classification of lymphoid neoplasms in mice. Blood. 2002;100(1):246-58.

39. Nikitin AY, Alcaraz A, Anver MR, Bronson RT, Cardiff RD, Dixon D, et al. Classification of proliferative pulmonary lesions of the mouse: recommendations of the mouse models of human cancers consortium. Cancer Res. 2004;64(7):2307-16.

40. Nolte T, Brander-Weber P, Dangler C, Deschl U, Elwell MR, Greaves P, Hailey R, Leach MW, Pandiri AR, Rogers A et al. . 2016. Nonproliferative and Proliferative Lesions of the Gastrointestinal Tract, Pancreas and Salivary Glands of the Rat and Mouse. J Toxicol Pathol 29(1 Suppl):1S-125S.
41. Renne R, Brix A, Harkema J, Herbert R, Kittel B, Lewis D, March T, Nagano K, Pino M, Rittinghausen S et al. . 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. Toxicol Pathol 37(7 Suppl):5S-73S.
42. Ring N, Meehan TF, Blake A, Brown J, Chen CK, Conte N, Di Fenza A, Fiegel T, Horner N, Jacobsen JO et al. . 2015. A mouse informatics platform for phenotypic and translational discovery. Mamm Genome 26(9-10):413-21.
43. Ringwald M, Eppig JT, Begley DA, Corradi JP, McCright IJ, Hayamizu TF, Hill DP, Kadin JA, Richardson JE. 2001. The Mouse Gene Expression Database (GXD). Nucleic Acids Res 29(1):98-101.
44. Rudmann D, Cardiff R, Chouinard L, Goodman D, Küttler K, Marxfeld H, Molinolo A, Treumann S, Yoshizawa K, INHAND Mammary Zs, Preputial, and Clitoral Gland Organ Working Group. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. Toxicol Pathol 40(6 Suppl):7S-39S.
45. Schofield PN, Bard JB, Booth C, Boniver J, Covelli V, Delvenne P, Ellender M, Engstrom W, Goessner W, Gruenberger M et al. . 2004. Pathbase: a database of mutant mouse pathology. Nucleic Acids Res 32(Database issue):D512-5.
46. Schofield PN, Gruenberger M, Sundberg JP. 2010. Pathbase and the MPATH ontology. Community resources for mouse histopathology. Vet Pathol 47(6):1016-20.

47. Shappell SB, Thomas GV, Roberts RL, Herbert R, Ittmann MM, Rubin MA, et al. Prostate pathology of genetically engineered mice: definitions and classification. The consensus report from the Bar Harbor meeting of the Mouse Models of Human Cancer Consortium Prostate Pathology Committee. Cancer Res. 2004;64(6):2270-305.
48. Smith B, Ashburner M, Rosse C, Bard J, Bug W, Ceusters W, Goldberg LJ, Eilbeck K, Ireland A, Mungall CJ et al. . 2007. The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration. Nat Biotechnol 25(11):1251-5.
49. Smith B, Ceusters W, Klagges B, Kohler J, Kumar A, Lomax J, Mungall C, Neuhaus F, Rector AL, Rosse C. 2005a. Relations in biomedical ontologies. Genome Biol 6(5):R46.
50. Smith B, Williams J, Schulze-Kremer S. 2003. The ontology of the gene ontology. AMIA Annu Symp Proc:609-13.
51. Smith CL, Goldsmith CA, Eppig JT. 2005b. The Mammalian Phenotype Ontology as a tool for annotating, analyzing and comparing phenotypic information. Genome Biol 6(1):R7.
52. Stemmer-Rachamimov AO, Louis DN, Nielsen GP, Antonescu CR, Borowsky AD, Bronson RT, et al. Comparative pathology of nerve sheath tumors in mouse models and humans. Cancer Res. 2004;64(10):3718-24.
53. Sundberg B, Schofield P, Gruenberger M, Sundberg J. 2009. A Data Capture Tool for Mouse Pathology Phenotyping. Vet Pathol. 46(6) 1230-1240
54. Sundberg JP, Berndt A, Sundberg BA, Silva K, Kennedy V, Bronson R, Yuan R, Paigen B, Harrison D, Schofield P. 2011. The mouse as a model for understanding chronic diseases of aging: the histopathologic basis of aging in inbred mice. Pathobiology of Aging & Age-related Diseases 1:71719.

55. Sundberg JP, Berndt A, Sundberg BA, Silva KA, Kennedy V, Smith RS, Cooper TK, Schofield PN. 2016. Approaches to Investigating Complex Genetic Traits in a Large-Scale Inbred Mouse Aging Study. Vet Pathol 53(2):456-67.
56. Sundberg JP, Sundberg BA, Gruenberger M, Schofield PN. 2010. A data capture tool for mouse phenotyping: obtaining a 'virtual second opinion' on skin and hair disease. Exp. Dermatol 19(6):595-595.
57. Sundberg JP, Sundberg BA, Schofield P. 2008. Integrating mouse anatomy and pathology ontologies into a phenotyping database: Tools for data capture and training. Mammalian Genome 19(6):413-419.
58. Thoolen B, Maronpot RR, Harada T, Nyska A, Rousseaux C, Nolte T, Malarkey DE, Kaufmann W, Küttler K, Deschl U et al. . 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. Toxicol Pathol 38(7 Suppl):5S-81S.
59. Turusov, VS (ed). Pathology of Tumours in Laboratory Animals. I. Part I – Tumours of the Rat. Lyon: IARC, 1973,
60. Turusov, VS (ed). Pathology of Tumours in Laboratory Animals. II. Tumours of the Mouse. Lyon: IARC, pp. 682, 1980.
61. Turusov, VS (ed). Pathology of Tumours in Laboratory Animals. III. The Hamster. Lyon: IARC, pp 472, 1983.
62. Turusov, VS and Mohr U (eds). Pathology of Tumours in Laboratory Animals. I. Tumours of the Rat, Second Edition. . Lyon: IARC, 1990, pp 766.
63. Turusov, VS and Mohr U (eds). Pathology of Tumours in Laboratory Animals. I. Tumours of the Rat, Second Edition. Lyon: IARC, 1994, pp 776.

64. Vahle J, Bradley A, Harada T, Herbert R, Kaufmann W, Kellner R, Mann P, Pyrah I, Rittinghausen S, Tanaka T. 2009. The international nomenclature project: an update. Toxicol Pathol 37(5):694-7.

65. Washington MK, Powell AE, Sullivan R, Sundberg JP, Wright N, Coffey RJ, Dove WF. Pathology of rodent models of intestinal cancer: progress report and recommendations. Gastroenterology. 2013 Apr;144(4):705-17. doi: 10.1053/j.gastro.2013.01.067. Epub 2013 Feb 12.

66. Weiss WA, Israel M, Cobbs C, Holland E, James CD, Louis DN, et al. Neuropathology of genetically engineered mice: consensus report and recommendations from an international forum. Oncogene. 2002;21(49):7453-63.

67. Yuan R, Tsaih S-T, Petkova SB, deEvsikova CM, Xing S, Marion MA, Bogue MA, Mills KD, Peters LL, Bult CJ et al. . 2009. Aging in inbred strains of mice: study design and interim report on median lifespans and circulating IGF1 levels. Aging Cell 8(3):277-287.

Figure Legends

Figure 1. Organizational Map of INHAND.

Figure 2. Example of a goRENI Manuscript.

Figure 3. Example of nomenclature map with INHAND terminology.

Figure 4. Schematic diagram describing post-composition strategy for lesions. Classes are taken from PATO, MPATH and MA and combined to form a formal statement describing the lesion and its location. A similar process may be used for gross pathology as well; PATO contains appropriate macroscopic qualifiers for this purpose, such as colour, texture, size and shape.

Figure 5. Screen shot of TCP's histopathology data entry user interface used to annotate IMPC strains.

Figure 6. Screen shot of TCP's histopathology data entry user interface. Note in the example for annotating a liver section, the dropdown selection list for MPATH Process Terms provides only terms applicable to liver histopathology.

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Figure 1 – Organizational Map of INHAND

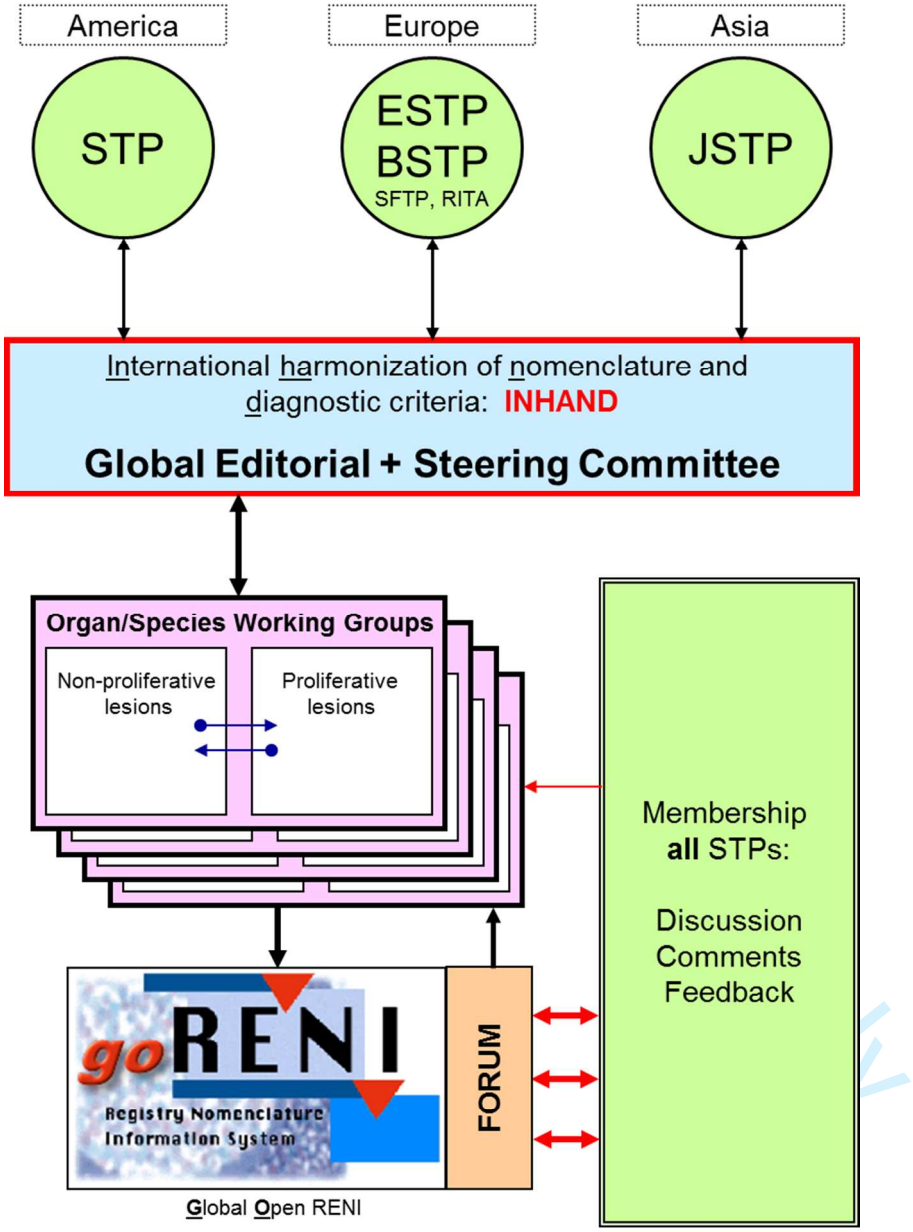


Figure 2 – Example of goRENI Manuscript

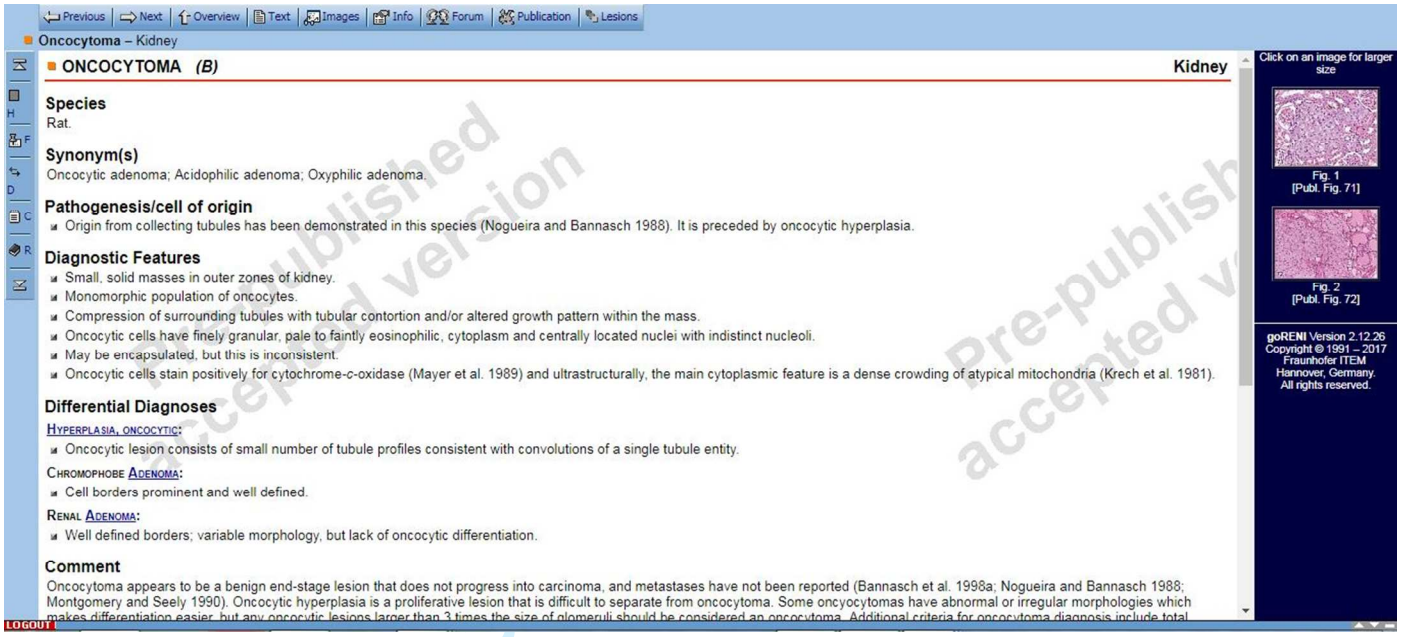
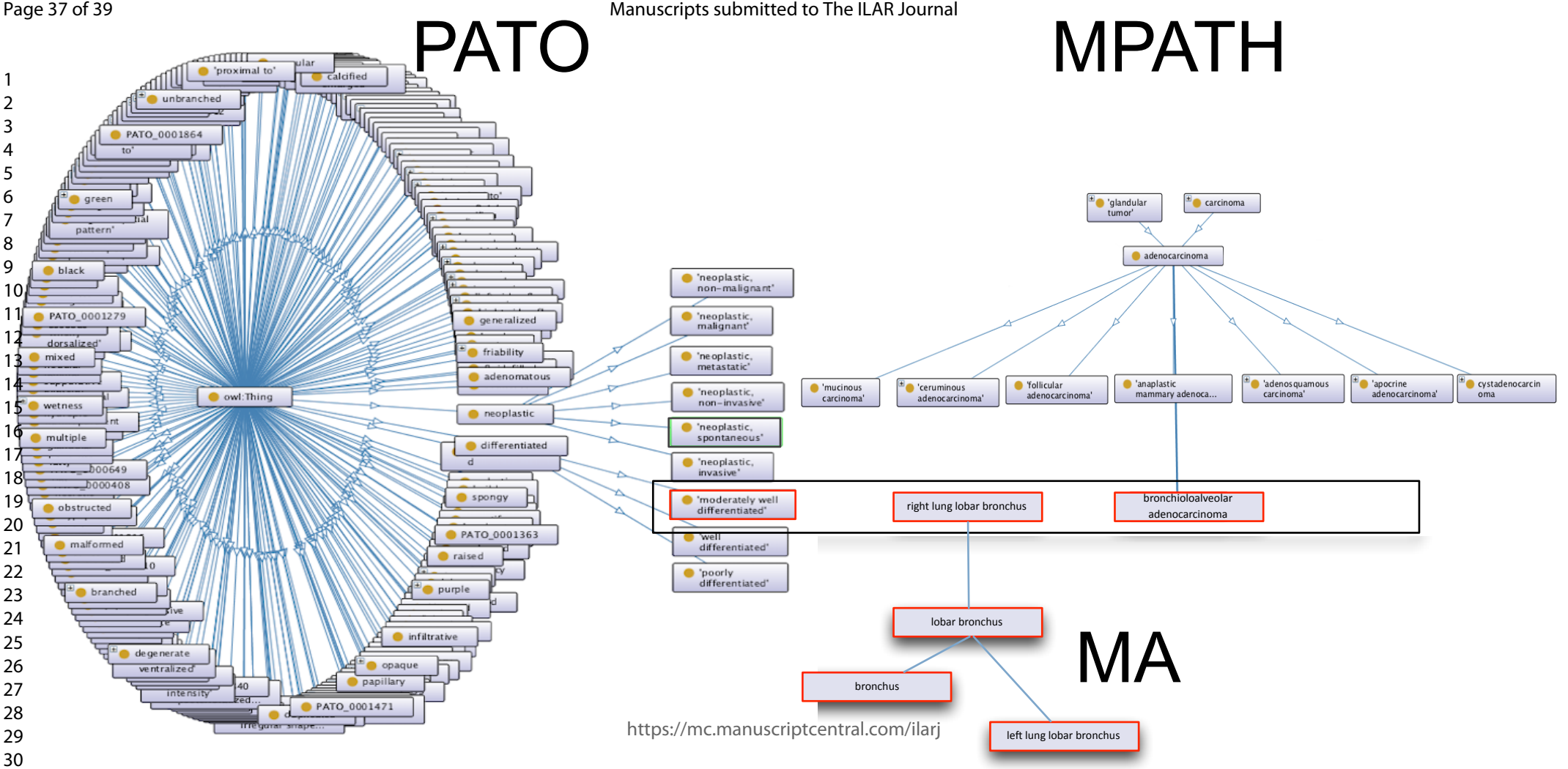


Figure 3 – Example of Nomenclature Map with INHAND Terminology

INHAND TERMINOLOGY			SEND CONTROL TERMINOLOGY						
Organ Working Group	Organ	Lesion	Body System MIBODSYS	Specimen (organ) MISPEC	Base Process MISTRESC	Severity MISEV	Distribution MIDISTR	Chronicity MICHRON	Characteristic(s) MIRESMOD
Hepatobiliary System	Liver	Bile duct hyperplasia		Liver	Hyperplasia				Bile duct
Hepatobiliary System	Liver	Cholangiofibrosis		Liver	Cholangiofibrosis				
Hepatobiliary System	Liver	Congestion		Liver	Congestion				
Hepatobiliary System	Liver	Crystals		Liver	Crystals				
Hepatobiliary System	Liver	Cysts, biliary (hepatic cysts)		Liver	Cyst(s)				Biliary
Hepatobiliary System	Liver	Degeneration, hydropic		Liver	Degeneration				Hydropic
Hepatobiliary System	Liver	Fibrosis		Liver	Fibrosis				
Hepatobiliary System	Liver	Focus of cellular alteration		Liver	Focus of cellular alteration				
Hepatobiliary System	Liver	Hepatocytes, glandular metaplasia		Liver	Metaplasia				Hepatocyte(s); Glandular
Hepatobiliary System	Liver	Hepatodiaphragmatic nodule		Liver	Hepatodiaphragmatic nodule				
Hepatobiliary System	Liver	Hyperplasia, endothelial		Liver	Hyperplasia				Endothelial
Hepatobiliary System	Liver	Hyperplasia, hepatocellular, non-regenerative		Liver	Hyperplasia				Hepatocellular; Non-regenerative
Hepatobiliary System	Liver	Hyperplasia, hepatocellular, regenerative		Liver	Hyperplasia				Hepatocellular; Regenerative
Hepatobiliary System	Liver	Hyperplasia, Ito cell		Liver	Hyperplasia				Ito cell
Hepatobiliary System	Liver	Hypertrophy, hepatocellular		Liver	Hypertrophy				Hepatocellular


PATO
MPATH
MA
owl:Thing
'proximal to'
calcified
unbranched
PATO_0001864
green
pattern'
black
PATO_0001279
dorsalized'
mixed
wetness
multiple
obstructed
malformed
branched
degenerate
ventralized'
intensity'
PATO_0001471
opaque
papillary
infiltrative
purple
raised
PATO_0001363
spongy
differentiated
neoplastic
adenomatous
friability
generalized
'neoplastic, non-malignant'
'neoplastic, malignant'
'neoplastic, metastatic'
'neoplastic, non-invasive'
'neoplastic, spontaneous'
'neoplastic, invasive'
'moderately well differentiated'
'well differentiated'
'poorly differentiated'
'glandular tumor'
carcinoma
adenocarcinoma
'mucinous carcinoma'
'ceruminous adenocarcinoma'
'follicular adenocarcinoma'
'anaplastic mammary adenoca...
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right lung lobar bronchus
bronchioloalveolar adenocarcinoma
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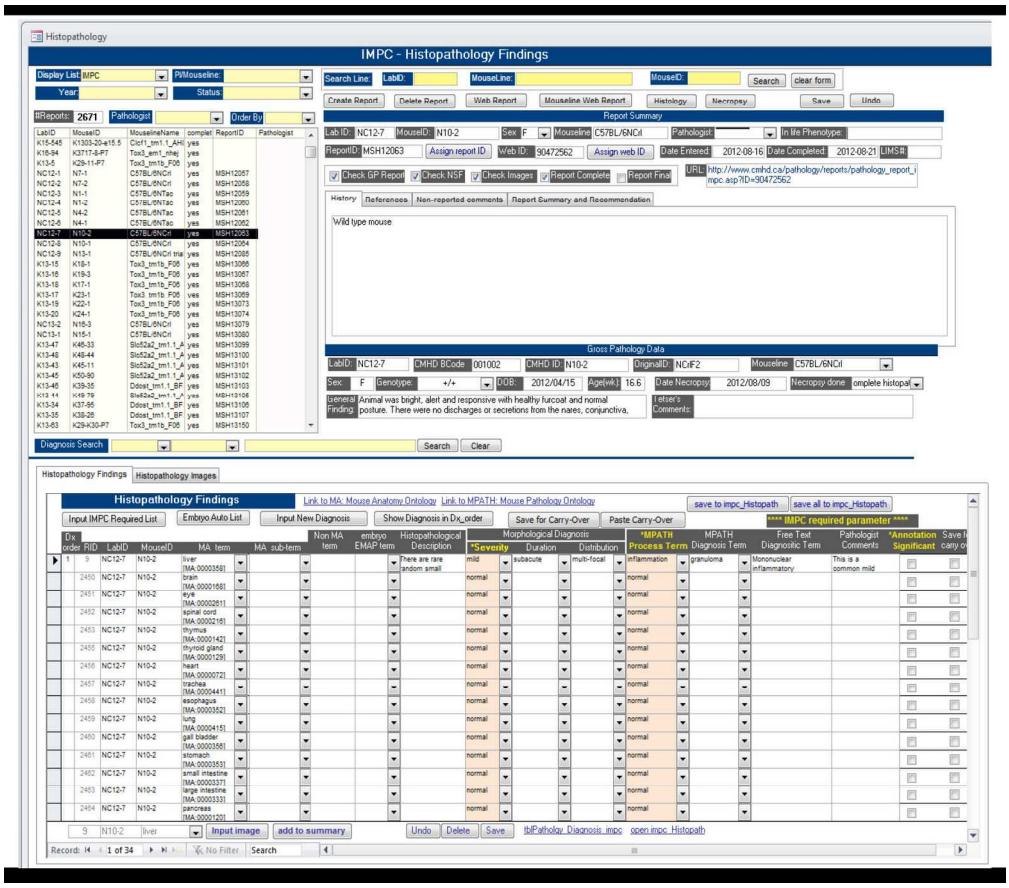
bronchus
left lung lobar bronchus



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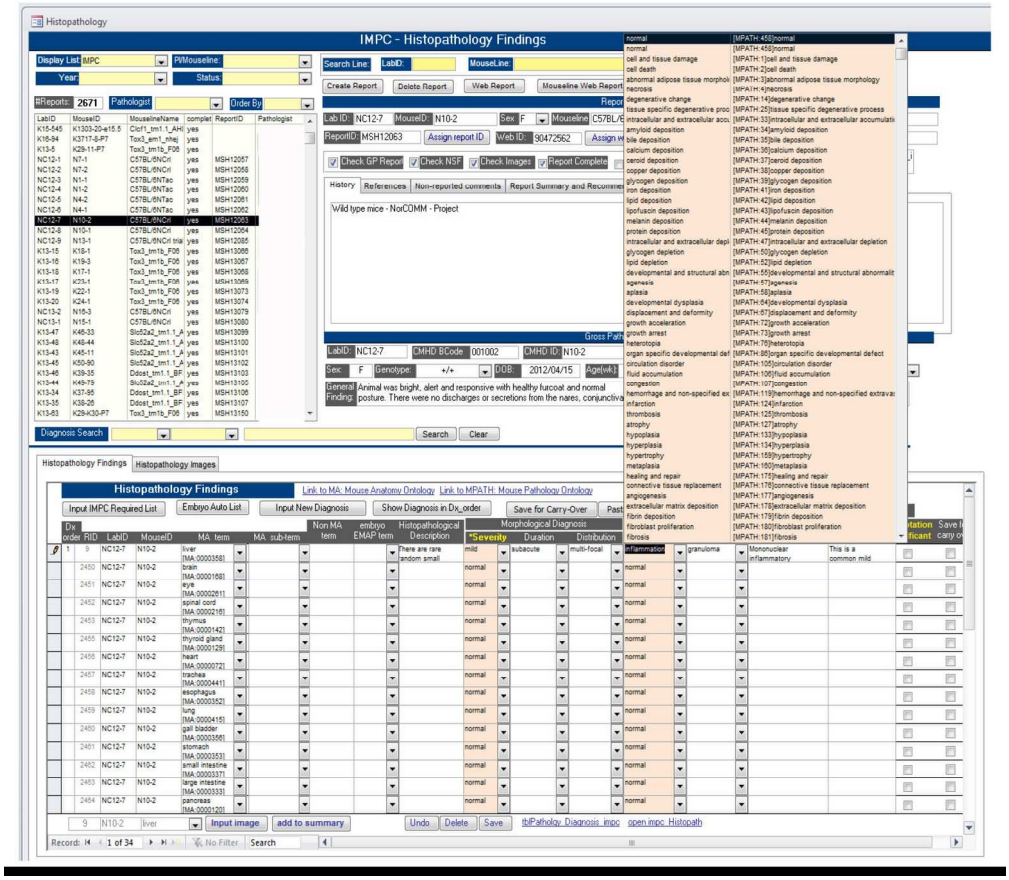

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191x169mm (300 x 300 DPI)