Journal of Genomes and Exomes

INTRODUCTORY EDITORIAL

A New Journal and a New Model for Structured Data Dissemination for an Era of Genomic Medicine

Stephen F. Kingsmore[1,2]

[1]Center for Pediatric Genomic Medicine, Children's Mercy Hospital, Kansas City, MO, USA. [2]Departments of Pediatrics, Obstetrics and Gynecology, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA.
Corresponding author email: sfkingsmore@cmh.edu

Summary: The *Journal of Genomes and Exomes* is a new, international, peer-reviewed, open-access, online publication. The *Journal of Genomes and Exomes* welcomes all structured reports of high quality genome, exome and gene panel sequences with attendant, detailed phenotypes. It also welcomes structured genotype-phenotype reports that confirm prior preliminary associations. It provides:

– Open-access—freely accessible online, authors retain copyright
– Fast publication times
– Peer review by expert, practicing researchers
– Post-publication tools to facilitate community-based meta-analysis for confirmation of genotype-phenotype relationships.

Keywords: genome, exome, DNA, diagnosis, disease, treatment, genomic medicine

Journal of Genomes and Exomes 2012:1 1–5

doi: 10.4137/JGE.S10090

This article is available from http://www.la-press.com.

Background

It is the seventh anniversary of the advent of next generation sequencing.[1] The profundity of this event is evidenced by a consequent drop in the cost to decode a human genome of 1153-fold in five years.[2] The $1000 human genome is likely to be attained in 2013 and the $100 genome in 2014.[3] While the bioscientific ramifications of inexpensive genomes will be wide-ranging, the most significant impacts of these technologies are likely to be felt in the areas of disease gene discoveries and implementation of genomic medicine. Disease gene discoveries will include the ~3500 Mendelian disorders of unknown cause and many common disease genes, particularly acting through rare, highly penetrant variants. Genomic medicine is a new, structured approach to disease diagnosis and management that prominently features genome sequence information.[4] It promises simultaneous, comprehensive differential diagnostic testing of likely genetic illnesses at time of presentation, accelerating molecular diagnosis, increasing rates of ascertainment, minimizing duration of empiric treatment and time-to-genetic counseling, and implementation of pharmacogenetically-informed treatment regimens.[5–7] Increasingly, genomic medicine will provide molecular diagnoses and drug/dosing selections that could not have been ascertained by conventional approaches by virtue of pleiotropic clinical presentation and genetic heterogeneity.[8–11] This will transform the diagnosis and treatment of genetic diseases from phenotype-driven, and genotype-assisted, to genotype-driven and phenotype-assisted. Indeed, the impending impact of dynamic electronic medical records and point-of-care genomes has been suggested to be the creative destruction of medicine.[12]

To put the $1000 genome in perspective, US health care costs in 2009 were $2.5 trillion, or $7,578 per capita.[13] They have risen by almost 6% per year for the past 20 years. This is likely to continue since there is evidence that additional spending on health care purchases greater patient satisfaction, possibly through increased access to technologies or more sophisticated facilities.[14] Given these underpinning economics, genomic medicine is cost effective today for some applications. It should be noted, however, that medically actionable genomes are quite a bit more costly than research-grade genomes. Sequence coverage must be higher.[15] Analysis, interpretation, confirmation and regulatory compliance are more exacting. Confirmatory testing is typically required. Nevertheless, there are already flourishing efforts in genomic obstetrics, neonatology and pediatrics, with regard to simple genetic diseases,[5–11,16,17] and genomic oncology, in tailoring chemotherapy to the specific somatic mutations in cancer biopsies.[18] Nor will the impact of genomic medicine be limited to high income countries. By virtue of consanguinity and relative genetic isolation of many micro-populations, the burden of genetic diseases—and potential benefits of genomic medicine—are higher in many low and middle income countries.[19]

The immediacy of genomic medicine is being substantially hastened by inexpensive sequencing of exomes (all protein coding exons) and targeted gene panels.[5,6,8,10,17,20–22] Exomes are about ten-fold less costly than whole genomes. Targeted gene panels are about three-fold less costly than whole exomes. In addition, their interpretation and actionability are much simpler. Besides the discovery and clinical testing of genetic disease and pharmacoligically relevant genes, these technologies are also expanding the applicability of sequence analysis. Examples include oligogenotype-phenotype relationships, such as epistasis, and ascertainment of the breadth of clinical and genetic heterogeneity in diseases.

Why Another Journal?

There are already quite a few peer-reviewed genetic, genomic and molecular medicine journals. It is a very reasonable question to ask, therefore, why add to this cacophony with yet another journal? Our rationale is simple and compelling. There are thousands of unpublished genomes and exomes. This number is growing exponentially. The current standard for publication of genomes and exomes is that they report strong evidence for a significant biologic insight or methodologic advance. For example, a trio with a plausible novel disease gene and high-likelihood pathogenic variant(s) is very difficult to publish currently without additional strong evidence of causality. Such evidence typically takes at least a year to generate, as was the case for a recent report of ours.[23] Since the throughput of genome and exome sequencing is very high, there are insufficient resources to generate strong evidence of causality for the majority of genotype-phenotype

observations, nor is the specialized expertise for gene-specific molecular biology typically resident in genome sequencing teams. Reports of new mutations or atypical presentations are typically not considered for publication unless presented in large bundles. This stringency appears defensible, except for the fact that some such information is medically actionable, and most such information has value for the implementation of genomic medicine in individual patients. But most compellingly, the most scalable and cost effective way to confirm novel genotype-phenotype associations is their replication in second, third and fourth families.

Scope of the *Journal of Genomes and Exomes*

The *Journal of Genomes and Exomes* seeks to fill this void by welcoming reports of high quality genome, exome and gene panel sequences with attendant, detailed phenotypes. Trios, quartets or pedigrees are favored. Images of clinical or imaging findings are encouraged. It also welcomes genotype-phenotype reports that replicate or refute prior preliminary associations. The *Journal of Genomes and Exomes* seeks to be an international forum for the initial description and subsequent community-based confirmatory reporting and synthesis of genotype-phenotype associations. The intent of the *Journal of Genomes and Exomes* is to allow fast, open-access, online, peer-reviewed publication of such findings. The journal facilitates community-based meta-analysis for confirmation or rebuttal of preliminary genotype-phenotype relationships by requiring the submission of supplementary, structured information in a flat file format. At the *Journal of Genomes and Exomes* we believe that the merit of articles should be assessed after, rather than before, their publication. The *Journal of Genomes and Exomes* therefore also welcomes submissions that provide expert aggregation and assessment of reports related to a specific gene, disease or phenotype. In particular, there are a number of disease mutations in the current literature that are incorrect. Submissions that correct such errors are welcomed. The long-term vision is to bring the data of the entire global genetic and genomic community to bear, using the wealth of opportunities offered online, to provide new, meaningful and efficient mechanisms for genome assessment.

Libertas Academia

The submission-to-print cycle of traditional journals is all too often a year. The burgeoning burden of journal subscriptions largely restricts access in countries with the highest burden of genetic illnesses.[19] As with all *Libertas Academia* journals, the *Journal of Genomes and Exomes* provides rapid electronic dissemination and unfettered internet access.

Requirements for Publication in the *Journal of Genomes and Exomes*

Manuscripts submitted for publication by the *Journal of Genomes and Exomes* must meet three quality requirements, which will co-evolve with genome sequencing and analysis technologies:

Bioethics

Reports must provide evidence of institutional approval or waiver by a human subjects research review board. Absent a waiver, informed consent and assent, if applicable, must have been obtained prior to data generation. Patient identifiers—other than DNA sequences—must not be included. Permission for photographic reproduction of patients must be documented. A structured template for submission of this information and an example will shortly be available.

DNA sequence data

Given the pace of change in genomic methods, the techniques used for DNA sequence generation and analysis must be described in sufficient detail to allow historical assessments of the quality of variant calling, genotyping and haplotyping for various types of variants. This exceeds the requirements of other journals, where the intent is not to provide genome scale variant information for future independent analysis. For example, the platform, version, number of gigabases of sequence, average quality score, length of reads, and whether singleton or paired sequences must be reported. Similar level of detail of enrichment and sequencing protocols, reagents and versions are required. Quality control measures should be documented, such as quantitative PCR-based estimation of fold enrichment. The minimum acceptable depth of sequence per sample is 100 GB for a human genome and 8 GB for an exome. Similarly, the software tools, versions and their parameterization, reference sequence versions, alignment and/or assembly

algorithms and paramaters, basecalling, variant calling, genotyping and functional assessments of variants should be detailed. The caveats of methods should be briefly described, such as the limits of indel sizes reliably detected or ability to call CNVs or gross rearrangements. All variant genotpes or haplotypes identified should be deposited in a public archive or appended as a flat file. Manuscripts should use standard gene, variant and accession nomenclature such as HGVS, OMIM, HGMD, ClinVar and/or dbSNP. A structured template for submission of this information and an example will shortly be available.

Quantitative phenotype information

Phenotypes should be described as quantitatively and clearly as possible. This exceeds the requirements of other journals, where the intent is not to provide phenotype information for future independent analysis. Demographics should be provided, without patient identifiers. A detailed family history of disease or other phenotype should be provided, preferably with a pedigree diagram. The clinical features should be described using structured terms and numbers, such as SNOMED-CT, if possible. Details of age of onset, duration, progression and severity should be included. Where there are objective severity scales, those should be used and cited. Material negative features should be noted. Relevant positive and negative clinical test results should be listed. In particular, biochemical and molecular genetic test results should be detailed. Where tests are panels, component results should be given. For complex tests such as ultrasound, MRI, CT scan, skeletal survey or EEG, the scope of the testing should be detailed. Relevant environmental and/or exposure information should be detailed. Incidental findings that are not relevant to the phenotype, but of value for future meta-analyses, should be presented where they are known values. Treatments and responses should be reported, including dosing. A structured template for submission of this information and an example will shortly be available.

It is worth reiterating that these requirements are necessary for community-based meta-analysis of material and so-called incidental findings for confirmation or rebuttal of suggested genotype-phenotype relationships. Our vision is to create a resource where all participants in genomic medicine can submit their findings and gain access to the findings of others.

In short, welcome to the *Journal of Genomes and Exomes*. We are keen to receive feedback regarding the journal's scope and requirements. As structured templates and examples are developed, we are keen to hear your comments and suggestions. This is intended to be a responsive community resource. Especially, we want lots of submissions. The greater the number of high quality exomes and genomes we publish, the more valuable will be this resource for discoveries and refinements in genomic medicine.

Acknowledgements

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