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Reports from CAGI: The Critical Assessment of Genome Interpretation

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New genomic and large-scale data hold the promise of revolutionizing our understanding and treatment of human disease, and are already influencing clinical practice. Multiple barriers stand between the acquisition of the data and fully realizing these and other benefits. In particular, we need powerful and well-characterized computational methods for deducing the phenotypic impact of genomic and system level perturbations. Many such methods have been developed, but currently, even though some are already deployed in clinical settings, we often remain ignorant of how they actually perform, as well as how and when they should be applied. Further, it is already clear that new and more sophisticated approaches must be developed to fully meet these challenges.

The Critical Assessment of Genome Interpretation (CAGI, \'kā-jē\) conducts community experiments to objectively assess computational methods for determining the phenotypic impacts of genomic variation. The primary goals are to establish the state of the art, to show where future progress may best be made, to highlight innovations and progress, and to build a strong collaborative community. In the CAGI experiments, participants are typically provided genetic variants and make blind predictions of resulting phenotypes. These predictions are evaluated against gold-standard experimental or clinical data by independent assessors. Four CAGI experiments have been conducted to date – a pilot in 2010, and three full-scale events in 2011, 2013, and 2016. Each edition of CAGI involves about 10 challenges. The experiment is conducted over a period of about a year, starting with the identification and development of suitable challenges, followed by a period during which participants are invited to submit their predictions, then a term in which the independent assessors evaluate the results, and concluding with a meeting to discuss the outcomes.

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CAGI challenges span a wide range of relationships between genetic variation and disease. For single base variants, there are challenges that address the problem of interpreting the impact of missense mutations on protein activity using a variety of molecular and cellular phenotypes; challenges that test the ability to predict the effect of mutations in cancer driver genes on cell growth; and challenges on the effect of single base variants on RNA expression levels and splicing (including Carraro, Minervini, et al., 2017; Xu, Tang, et al., 2017; Zhang, Linch, et al., 2017; Niroula and Vihinen 2017; Katsonis and Lichtarge 2017; Capriotti et al. 2017; Pejaver et al. 2017; Yin et al. 2017; Tang et al., 2017; Tang and Fenton, 2017; Kreimer, Zeng, et al., 2017; Beer, 2017; Zeng, Edwards, et al., 2017). At the level of full exome and genome sequence, there are challenges that assess methods for assigning complex traits phenotypes and that evaluate ability to associate genome sequence an extensive profile of phenotypic traits (including Daneshjou, Wang, et al., 2017; Giollo, Jones, et al., 2017; Pal, Kundu, et al., 2017a; Laksshman, Bhat, et al., 2017; Wang, Chang, et al., 2017; Daneshjou, Gamazon, et al., 2014; Cai, Li, et al., 2017). CAGI also included challenges in which participants were asked to identify causative variants for rare diseases in gene-panel, exome and whole genome sequence data (including Chandonia, Adhikari, et al., 2017; Kundu, Pal, et al., 2017; Pal, Kundu, et al., 2017b). Many challenges have focused on cancer, given its prevalence and the impact of genetics.

This special issue of *Human Mutation* contains a selection papers reporting the assessments of challenge results, as well as papers from some individual participating teams, describing their methods and the results obtained. Most papers report on the recent challenges, from CAGI4, held in 2016. As CAGI best helps further development when challenges reoccur year after year, some manuscripts discuss results from the earlier editions of CAGI and their development over time.

Together, these results from CAGI offer powerful insights into the appropriate level of confidence to place in variant annotations and interpretation methods, and which classes of approaches are most suitable for a particular application. They reveal limitations of current data collection and analysis approaches and point to areas for future research and new approaches.

The fifth CAGI edition is presently underway. Full information about this and the previous CAGI editions is at http://www.genomeinterpretation.org.

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