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NINDS stroke genetics network (SiGN) experience with the causative classification system

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Lanfranconi and Markus (1) recently described a single-center experience using the Causative Classification System (CCS) in cases genotyped in the Wellcome Trust Case Control Consortium-2 and report high agreement rates with TOAST subtyping. They conclude that the web-based CCS appears suitable for multicenter studies. We would like to outline the ongoing NINDS-funded Stroke Genetics Network (SiGN) experience using the CCS. As of March 10, 2012, physician adjudicators have classified 15 252 cases in SiGN, of which 11 021 currently have TOAST subtyping in the database. All cases were adjudicated using a study-specific version of CCS, which has been slightly modified to facilitate study coordination (2). Every adjudicator has been trained and certified using an online education module. SiGN currently has 53 certified adjudicators across 10 countries at 21 centers, including the St. George's Hospital, London. When planning SiGN, investigators considered central adjudication by a committee analogous to what was done in the Ischemic Stroke Genetics Study (ISGS) (3). Ultimately, a decentralized approach to subtyping was adopted because it was seen as time efficient, with more adjudicators operating in parallel. For centers where medical records are in English, the SiGN Phenotype Committee provides quality control through central readjudication of a random sample of cases. For centers where medical records are in a language other than English, the Phenotype Committee provides the center with a list of cases selected at random for readjudication by a local CCS-certified physician.

The web-based CCS, which allows for online training, certification, and data entry, is a practical way of aggregating thousands of cases across the globe in a rule-based manner,

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while simultaneously harmonizing and structuring phenotype data. Having large numbers of cases of ischemic stroke subtyped into categories of presumed etiology has been essential for discovering replicable loci in genome-wide association studies (4).

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