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Authoring and Peer Review

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Medical Genetics Summaries is a growing collection of articles describing how genotypes play a role in an individual's response to drugs or predisposition to disease. This pharmacogenomics-focused resource brings clinically relevant information to point of care. Each chapter focuses on one drug and the structured format of each summary includes review and synthesis of peer-reviewed research about the variants and their impact in drug metabolism and action, strategies for genetic testing and access to available therapeutic recommendations from medical and professional societies. Medical Genetics Summaries are based on authoritative sources, driven by professional and medical guidelines, actionable, and undergo an extensive review process as described below.

Editorial Oversight

The MGS editors advise on subject matter, guide the project through developments in the field, provide final approval before publication, and assist in recruiting reviewers and resolution of key issues that may arise during the review process.

Selection of Topics

The selection of topics for new MGS chapters is influenced by drugs approved by the U.S. Food and Drug Administration (FDA) that have pharmacogenomic biomarkers in the label, the availability of clinical testing for drug response, the needs of the community, and input from the editors.

To identify new drugs not yet covered in MGS, the author consults the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labeling". To prioritize the selection of new MGS chapters, the author checks the Genetic Testing Registry (GTR) for clinically available genetic tests for drug responses that lack guidelines or summary information from sources like PharmGKB or CPIC. The author takes into consideration the current needs of the community, for example adding summaries that support National Institutes of Health (NIH) initiatives like the All of Us research program's Medicine and Your DNA report, and the NIH Helping to End Addiction Long-term (HEAL) Initiative.

Upon the release of a new MGS chapter to the production site, an excerpt is displayed in the relevant GTR and MedGen drug response records. Reciprocal links between MGS, GTR, MedGen, and other National Center for Biotechnology Information (NCBI) resources are also added for better integration and accessibility.

Structured Format

Each MGS drug response chapter follows a structured format and draws from available published research evidence. Each summary has one drug section and one or more gene sections, depending on how many genetic factors have been identified to influence drug metabolism and action.

1. The introductory paragraphs detail the drug, its clinical uses, and how genetic variants influence an individual's response to the drug. Dosing recommendations from the FDA drug labels and practice guidelines from authoritative professional and medical societies are also presented.
2. The drug section begins with a description of the drug, including drug class, mechanism of action, indications for use, and common side effects. This is followed by a discussion on the factors that influence the drug response.
3. The gene section reviews important facts on the gene's role in drug metabolism or action, describes the genetic variants and the predicted impact on enzyme activity and how they influence the individual's response to the drug. It also discusses common or clinically significant variants, including their prevalence across different ethnic populations.
4. Linking genetic variation with treatment response covers in more detail the specific evidence and outcomes for variation in the gene(s) from the previous section and predicted individual responses to the drug. Key variants and alleles with impact on drug efficacy or adverse effects are discussed as well as emerging evidence that may be informative though it is not yet clinically actionable.
5. The "Genetic Testing" section describes available genetic testing options and links to currently available genetic tests for the gene(s) and drug response listed in the NIH GTR. The GTR is a resource of descriptions of clinical and research tests that includes phenotypes, test targets, methodologies and instructions on how to order the test from the laboratory.
6. The Gene-drug interactions section provides a list of interactions between the gene(s) of note and other medications, including those used in other indications separate from the current chapter. Additional resources to learn more about other medications that may be impacted by variations in the same gene are also included.
7. The "Therapeutic Recommendations based on Genotype" excerpts clinically actionable information, such as dosing recommendations from the FDA drug label, and therapeutic recommendations from pharmacogenetic societies (for example, the Clinical Pharmacogenetics Implementation Consortium [CPIC], the Canadian Pharmacogenomics Network for Drug Safety [CPNDS], The Dutch Pharmacogenetics Working Group [DPWG]) and medical societies (for example, the American Society of Clinical Oncology [ASCO], the American College of Medical Genetics and Genomics [ACMG], the National Comprehensive Cancer Network [NCCN]). The MGS does not create guidelines or recommendations.
8. The nomenclature table provides information on different terms used for genetic variants. Commonly used terms and historic terms, like the star allele nomenclature, are linked to the official Human Genome Variation Society (HGVS) terms and rs identifiers when available. The table also includes links to relevant resources like ClinVar, dbSNP, and the Pharmacogene Variation (PharmVar) Consortium.
9. Expert reviewers are a vital part of MGS and are acknowledged in every chapter. Information and access to previous versions of the summary is displayed.

Writing Process

Each summary is authored by our in-house senior medical writer, who holds a PhD with professional experience in pharmacogenomics. All phases, from authoring to production, are tracked in an internal ticket management system.

To create the first draft of a summary:

1. The author consults the most recent FDA drug label for the drug. Additionally, to gain a better understanding of the drug's context of use and the impact of genetic factors, the author uses NIH resources and other clinical sites, such as UpToDate.
2. Next, the author identifies key guidelines and primary research papers, using PubMed Clinical Queries, PubMed, CPIC, and The Pharmacogenomics Knowledgebase (PharmGKB).

3. Finally, the author searches PubMed for the most recent publications. Firstly, to find content that has not yet been cited by guidelines; and secondly, to identify external reviewers who are actively involved in relevant research.

Internal Review

Each summary undergoes internal review involving one or 2 NCBI staff members with experience in genetic counseling or molecular genetics. Once the author has finalized the first draft of a summary, it is submitted for internal review, along with the key supporting guidelines. The internal reviewers perform the first round of expert review, utilizing track changes to ask questions, provide suggestions and make corrections. This process is documented in a ticket management system, including all versions of the document and comments from the author and reviewers.

External Review

Following the internal review, each summary goes through a scientific peer-review process involving between 2–9 experts from outside NCBI. The external review includes at least one clinical specialist experienced in prescribing the drug and with published papers on its use, and one laboratory professional experienced in pharmacogenomics. Experts are selected based on their clinical or laboratory experience and relevant publications in PubMed and any potential conflicts of interest are displayed to avoid real or perceived bias. The comments from expert reviewers are retained in our internal records. After the summary is released to production, all current and previously published versions are stored in the document management system, allowing public access.

Finalizing the Summary

Once all the review comments are reconciled, the summary undergoes in-house copyediting before public release.

Updates

Summaries are scheduled to be updated every 4–6 years or whenever there is an update to guidelines from which excerpts have been taken for the summary. Minor updates (revisions) may be needed to update citations or external links to reference materials.

Major Updates

A major update involves review and update of all sections of the given chapter; it then undergoes the full review cycle described above: drafting and revision internally, external peer review (minimum 2 reviewers), editorial board review (minimum 2 editors), copy editing and then publication. The new version will be differentiated by a new date and increase the version index by one integer (for example version 2.1 to 3.0).

Minor revisions

Minor revisions will often impact only one or two sections (for example, one reference or a single table) and do not involve edits to the whole chapter. Minor edits are reviewed internally and copy edited before publication. Minor updates are indicated by an increase in the count following the primary version number (namely, from version 1.0 to 1.1 for a minor edit).

Previous versions and changes

Both major and minor updates will be noted in the Version history in the article. Minor revisions will state in summary what was addressed in the version. For example: 'This chapter was revised on January 5, 2021 to update a link for reference number 42; v.2.1.'

When previous versions of the chapter are made available as PDFs, only one file is provided per major version, the most recent iteration. For example, if a chapter had 4 minor revisions for citation updates, v. 1.4 will be available as the previous version when version 2.0 is published.

Archive

Summaries will be archived if the FDA withdraws approval for the drug. Archived summaries display notices to alert the user that the summary is archived, the information is not maintained and may be out of date, serving as a historical reference only. The notices include the statement: NOTE: ARCHIVED ON [date] BECAUSE [drug name] IS NO LONGER LICENSED FOR USE IN THE USA. THIS SUMMARY IS FOR HISTORIAL REFERENCE ONLY AND WILL NOT BE UPDATED.

Summaries are not deleted, and they remain publicly available for display. Please note that archived summaries are not listed in the table of contents, though they will remain indexed in PubMed.

Version history

Each summary displays the created date and the date of its last update or revision. Once a version of the summary is published and made publicly available, the date of publication is logged and displayed.

Access to major versions of the document is provided via links in the Version history section.

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