Anthem

Medical Policy

Subject: Saliva-based Testing to Determine Drug-Metabolizer Status
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Description/Scope

This document addresses the use of saliva-based testing to determine drug-metabolizer status. This document does not address the collection of saliva for genetic testing (for example, Genecept™ Assay).

Note: This document does not address genotype testing or other multi-gene testing for polymorphisms to determine drug-metabolizer status. Criteria for genetic testing for polymorphisms to determine drug-metabolizer status are found in applicable guidelines used by the plan.

Position Statement

Investigational and Not Medically Necessary:

Saliva-based testing to determine drug-metabolizer status is considered **investigational and not medically necessary** for all indications.

Rationale

Interpersonal differences in response to drugs are common. These differences are due in large part to variations in the cytochrome P450 (CYP450) family of enzymes which is responsible for oxidative drug metabolism in the liver. The activity levels of specific CYP450 enzymes (CYPs) in the liver can be assessed by measuring the concentrations of their particular drug substrates and metabolites present in saliva. Subjects can be given a cocktail of drugs to ingest that are substrates ("probes") for a number of CYPs of interest. Subjects then submit a saliva sample and metabolites of these probes by CYPs are measured. The ratio of the probe concentration to the concentration of probe metabolite is considered to be the metabolic phenotype for a specific enzyme. Using this information, a subject's drug metabolizer status can be determined. With knowledge of a subject's metabolizer status, a clinician can personalize the selection and dosage of drug prescribed to maximize efficacy based on the ability of the individual's body to break down the drug. The cocktail approach to metabolic phenotyping has been widely studied as it allows for the *in vivo* assessment of multiple pathways of drug metabolism at one time. Several phenotyping cocktails have been developed including the Geneva cocktail and the Basel cocktail.

In a 2020 study by Rollason and colleagues, the authors reported on the Geneva cocktail which is comprised of a specific probe for six different CYPs (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A) and one for P-gp. In this study the Geneva cocktail was evaluated in a group of 265 healthy adult volunteers in three different populations from Ethiopia, Oman, and the Czech Republic. The purpose of the study was to report safety of the cocktail. The Geneva cocktail is made up of a combination of substances (caffeine, bupropion, flurbiprofen, dextromethorphan, midazolam, and fexofenadine) in a single capsule and an additional tablet of omeprazole. Participants received the cocktail and were tested at 2, 4, and 6 hours following administration. Subjects reported adverse events and standard blood spots were taken for evaluation. There were four reported adverse events including 1) dizziness, lack of concentration and headache, 2) numbness of both hands and feet, 3) nausea and abdominal heaviness, and 4) a localized erythematous macular nonpruritic rash on both thighs. It was concluded the adverse events using this low-dose phenotyping cocktail were mild to moderate and all resolved spontaneously.

In two studies from 2021, Lenoir and colleagues assessed the impact of acute inflammation and SARS-CoV-2 infection on CYP450 activity using the Geneva phenotyping cocktail. These were prospective observational studies conducted in 30 and 28 subjects, respectively. Hip surgery was the acute inflammation model (Lenoir, 2021a), and the probe drug cocktail was administered orally before surgery, day 1 and day 3 post surgery and at discharge. Capillary blood samples were collected 2 hours after cocktail intake to assess metabolic ratios (MRs) of the six different CYPs. It was determined that inflammation modulated activity of the CYPs in an isoform-specific manner, with different magnitudes and kinetics for each. In the study of SARS-CoV-2 (Lenoir, 2021b), individuals received the Geneva cocktail orally during the first 72 hours of hospitalization for COVID-19 and after 3 months, with blood samples collected 2 hours after cocktail administration to assess MRs of the same six CYPS. As in the previous study, CYP activity was modulated in an isoform-specific manner by SARS-CoV-2 infection. In both studies, the authors concluded that inflammation or SARS-CoV-2 infection could have a clinically relevant impact on the pharmacokinetics of CYP substrates. However, these were small studies and confirmation of multivariable statistical modeling findings within a larger sample size is needed, allowing for possible adjustment with other covariates.

While most published studies address phenotyping using blood and plasma samples, saliva sampling is also being evaluated in metabolic phenotyping studies involving several CYP450 enzymes. In a meta-analysis of four studies in which caffeine and its metabolite paraxanthine were measured in saliva, plasma and urine of 78 subjects, Fuhr and colleagues (1994) found that the paraxanthine/caffeine ratios in saliva and plasma were highly correlated and provided a better estimate of CYP1A2 activity than urine ratios.

Urine collection over an 8- to 10-hour period following ingestion of dextromethorphan is one process for metabolic phenotyping. However, sometimes urine collection may not be desirable, for example in those with renal disease, or in children. In 1991 Hou and colleagues evaluated the use of saliva for metabolic phenotyping of CYP2D6 in 62 healthy volunteers, with 61 subjects included in the final analysis. In this study, urine collections were also taken for comparison. All participants received one dose of dextromethorphan, then a 5 to 10 ml saliva sample was collected over a 2- to 5-minute period. Saliva was collected by the initial 12 subjects at 30 and 60 minutes for 8 hours after taking dextromethorphan. The next 12 subjects collected saliva samples at 2 and 3 hours after taking dextromethorphan. The last 38 subjects collected saliva at 3 hours following ingestion of dextromethorphan. They found that salivary dextromethorphan/dextrorphan ratios showed a significant correlation with urinary ratios and enabled differentiation of CYP2D6 poor metabolizers from intermediate and extensive metabolizers. However, intermediate and extensive metabolizers could not be separated on the basis of salivary results. Further study is necessary to determine improvement in net health outcomes.

In a randomized crossover study of 16 healthy volunteers, Donzelli and colleagues (2014) sought to develop another cocktail (the

Basel cocktail) based on probe drugs that are widely used in clinical practice. The authors also sought to determine whether other sampling methods such as dried blood spots or saliva samples could be used to simplify the sampling process. The cocktail consisted of caffeine, efavirenz, losartan, omeprazole, metoprolol and midazolam in different combinations. The Basel cocktail was tested for simultaneous phenotyping of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in plasma, dried blood spots and saliva. In dried blood spots, only caffeine, paraxanthine, omeprazole, 5-OH-omeprazole, efavirenz, and midazolam were quantified. In saliva, all analytes except for caffeine, paraxanthine, omeprazole, 5-hydroxyomeprazole, and metoprolol were too low to quantify reliably. While use of dried blood spots and saliva samples seems feasible for phenotyping of selected CYP isoforms, further study is necessary to confirm these results, particularly in differing population groups.

Background/Overview

Human CYP450 enzymes in the liver are responsible for metabolizing approximately 50% of commonly used drugs. The activity of CYP450 enzymes is highly variable between individuals and is determined by genetic variants, endogenous mediators and environmental influences such as nutrients or interacting medications. Differences in drug metabolism can lead to challenges in optimizing dosage for an individual patient. Variations in CYP450 enzyme metabolic activity can be associated either with drug toxicity if too little is metabolized or with an insufficient pharmacological effect if too much is metabolized. Genotyping can only assess genetic factors contributing to CYP450 enzyme activity variation while phenotyping can assess the net effect of all influencing factors on CYP450 activity. Metabolic phenotyping uses specific probe drugs to obtain information about real-time activity of CYP450 drug-metabolizing enzymes in an individual.

Definitions

Cytochrome P450: Refers to a family of 60 different enzymes involved in drug and toxin metabolism.

Metabolize: Refers to breaking down a drug so that it is no longer clinically active.

Metabolite: Substance formed during the process of metabolism.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

84999	Unlisted chemistry procedure [when specified as a phenotype test of CYP450 enzymes for drug-metabolizer status using a saliva specimen]

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. Derungs A, Donzelli M, Berger B, et al. Effects of cytochrome p450 inhibition and induction on the phenotyping metrics of the basel cocktail: a randomized crossover study. Clin Pharmacokinet. 2016; 55(1):79-91.
2. Donzelli M, Derungs A, Serratore M-G, et al. The basel cocktail for simultaneous phenotyping of human cytochrome P450 isoforms in plasma, saliva and dried blood spots. Clin Pharmacokinet. 2014; 53(3):271-282.
3. Fuhr U, Rost KL. Simple and reliable CYP1A2 phenotyping by the paraxanthine/caffeine ratio in plasma and in saliva. Pharmacogenetics.1994; 4(3):109-116.
4. Hou ZY, Pickle LW, Meyer PS, Woosley RL. Salivary analysis for determination of dextromethorphan metabolic phenotype. Clin Pharmacol Ther. 1991; 49(4):410-419.
5. Lenoir C, Daali Y, Rollason V, et al. Impact of acute inflammation on cytochromes P450 activity assessed by the Geneva cocktail. Clin Pharmacol Ther. 2021a; 109(6):1668-1676.
6. Lenoir C, Terrier J, Gloor Y, et al. Impact of SARS-CoV-2 infection (COVID-19) on cytochromes P450 activity assessed by the Geneva cocktail. Clin Pharmacol Ther. 2021b; 110(5):1358-1367.
7. Rollason V, Mouterde M, Daali Y, et al. Safety of the Geneva cocktail, a cytochrome P450 and P-glycoprotein phenotyping cocktail, in healthy volunteers from three different geographic origins. Drug Saf. 2020; 43(11):1181-1189.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Pharmacogenomics Testing.
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    - LCD L38435. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38435&ver=10&keyword=Polymorphisms&keywordType=starts&areaId=all&docType=F&contractOption=all&sort

By=relevance&bc=1. Accessed on December 22, 2023.

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Document History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Description, Rationale and References sections.
Reviewed	02/16/2023	MPTAC review. Updated Rationale, Background/Overview, and References sections.
New	02/17/2022	MPTAC review. Initial document development.