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The Search for Biomarkers and Endophenotypes in Functional Gastrointestinal Disorders

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In large part in response to the frustration in the development of new, cost-effective pharmacological therapies for functional gastrointestinal disorders (FGID), there has been a recent, 2-pronged effort aimed at developing generally acceptable patient reported outcomes,[1] and to identify and validate so-called biomarkers for the various disorders.[2] Over the past decade, there has been a surge in interest in the development of biomarkers in many disease areas, including cancer and cardiovascular disease (exclusively in so-called "organic disorders"), in the hope that such measures could improve diagnosis and accelerate drug development.[3,4] Biomarkers have been defined as "a characteristic that is measured and evaluated as an indicator of normal biological processes, pathogenetic processes, or pharmacologic responses to a therapeutic agent."[4] An implicit assumption of the biomarker approach is the specificity of a particular biomarker for a specific disease or disorder, or a subset of patients with the disease. The interest in biomarkers has been primarily driven by the search for "surrogate endpoints," which could make clinical trials more cost effective, at a time of dramatically increased number of candidate drugs. A surrogate endpoint "is a biomarker that is intended to substitute for a clinical endpoint and that is expected to predict clinical benefit."[3,5] The fact that the existence of a valid biomarker is associated with the availability of more new drugs for a particular disease supports the validity of this concept.[5] There are many examples of successful application of the biomarker approach, including HIV viral load for approval of antiviral drugs, tumor size and progression-free interval for approval of anticancer drugs, and low-density lipoprotein cholesterol for approval of statins. There are other commonly used surrogate endpoints (such as blood pressure for drugs aimed at reducing stroke and myocardial infarction; or glycosylated hemoglobin for approval of antidiabetic drugs) where the usefulness has recently been questioned, and other areas where it has failed.[5]

Can this approach, which has been so successful in many "organic" diseases with fairly well understood pathophysiology, be applied to the large number of FGID, in which the pathophysiology is largely unknown, and the majority of which remain defined by ever-changing symptom criteria? This question was addressed by a recent conference co-organized by the American Neurogastroenterology and Motility Society and the Office of Translational Sciences at the US Food and Drug Administration (Digestive System Motility Biomarker Qualification Workshop, FDA White Oak Campus, Silver-spring, MD, September 23–24, 2010). Given the complex, polygenic nature of brain–gut disorders such as irritable bowel syndrome (IBS) or functional dyspepsia (FD), it is highly unlikely that the identification of a single biomarker (eg, increased mucosal mast cell count or increased intestinal permeability) would be able to explain a large proportion of the variance of such syndromes. However, it would seem that among the 40 or so FGID, those syndromes where there is an objectively identifiable abnormality in gastrointestinal transit, objective, standardizable, and easily performable measures of such abnormalities (such as gastric emptying tests or colonic transit measures) would make ideal biomarkers. Indeed, Camilleri[2] has recently summarized the evidence supporting the utility of noninvasive colonic transit

measurements for drug development for colonic motility disorders, including chronic constipation. Similar efforts are underway to validate a gastric emptying test for gastroparesis.[6,7] However, the problem with FGID is the fact that such objective abnormalities as regional delays in GI transit are only present in a subset of patients with a particular symptom-defined syndrome, who report the same symptoms as patients without the transit abnormality. As a consequence, there is a relatively weak correlation between such transit abnormalities and symptoms, and between drug-induced improvement of transit abnormalities and symptom improvement. For example, identical symptoms of dyspepsia can be present with or without delayed gastric emptying, and symptoms of constipation are reported by patients with completely normal colonic transit.

In FGID, symptom perception, symptom severity, and quality-of-life impairment are influenced by many factors in addition to transit abnormalities, including enhanced perception of visceral signals and affective comorbidity. For example, in FD it has been shown that such non–GI-related components may even be more important in determining symptom severity than objective, physiologic abnormalities, such as gastric emptying or gastric sensitivity.[8,9] Even in the presence of an objective biomarker, such as delayed gastric emptying in diabetic gastroparesis, such other factors may determine symptom severity. Would a drug that is effective in improving or normalizing delayed colonic transit in patients with colonic inertia (eg, a small subset of all patients reporting the symptom of chronic constipation) also be effective in patients with the same clinical diagnosis but normal colonic transit? Or, similarly, would a prokinetic drug that accelerates gastric emptying in patients with diabetic gastroparesis (caused by specific diabetes-related molecular pathology) also be effective in treating patients with similar symptoms of dyspepsia symptoms, but normal gastric emptying, even though subjective symptom severity in the latter group may be primarily related to central pain amplification? For complex disorders reflecting a dysregulation of the brain–gut axis, will it be necessary to have several surrogate endpoints (eg, 1 reflecting central pain amplification, and 1 altered GI transit), with changes required in all of them for a successful drug? Before rushing to unleash a new era of biomarkers and surrogate endpoints in FGID, these questions deserve careful consideration and validation.

In parallel to the extensive use of the biomarker (surrogate endpoint) approach in biomedical drug development, there has also been a surge in the identification and validation of so-called intermediate or endophenotypes, a term that has often been used synonymously with the term biomarker. However, in contrast with the biomarker concept, which has arisen in the field of biomedicine, the endophenotype concept has arisen in the field of psychiatry (a field of clinical neuroscience) in an attempt to find latent phenotypic constructs that are intermediate between the complex clinical symptom presentation and genes.[10] Rather than pursuing the futile search for an association between a complex, polygenic human syndrome and single genes, the endophenotype approach aims to correlate 1 or several genes, as well as interacting environmental factors, with less complex, neuropsychological or neurobiological constructs, or latent variables. It has been assumed that the closer the endophenotype is related to specific biologic brain mechanisms, the greater the association with a particular gene or network of genes would be.

From its early conceptualizations of single endophenotypes, which show associations with individual candidate genes, the field has rapidly moved into the direction of identifying multilevel, multivariate endophenotype networks, which can be correlated with gene networks identified by genome-wide association studies.[11] In contrast with the disease-specific biomarker, endophenotypes are inheritable, and therefore expected to be present in asymptomatic relatives; they are not syndrome specific, but can be involved in the pathophysiology of multiple, seemingly unrelated disorders.[12] In pain research, the concept

of individual pain syndromes being composed of a mosaic of shared endophenotypes has been proposed.[13] Brain endophenotype candidates that have been proposed for FGID include measures of sensorimotor gating, brain circuits identified by functional magnetic resonance imaging, mediating emotional arousal and stress responsiveness, selective attention to threat or incorrect prediction of symptom severity ("catastrophizing"), or recently reported changes in brain structure identified by structural magnetic resonance imaging techniques.[14,15] Such brain endophenotypes are unlikely to be specific to a symptom-defined syndrome such as IBS, FD, or noncardiac chest pain, but would be expected to be seen in a wide range of symptom-based disorders, ranging from psychiatry and chronic pain to gastroenterology. Distinct clinical presentations are likely to arise from distinct patterns of endophenotypic networks.

In summary, there is clearly a need to identify and validate disease-specific biomarkers as surrogate endpoints for drug development for a selective group of FGID, which are characterized by objective, reproducible abnormalities in regional gastrointestinal transit, in which these regional transit abnormalities explain a large part of the variance in symptom severity, and which are highly correlated with patient reported outcomes. Significant progress is being made in this field.[2] At the same time, there is an equally important need to identify objective, reproducible brain endophenotypes, which are highly correlated with central pain amplification and symptoms of pain and discomfort. (It is likely that some of these brain endophenotypes have homologues in the enteric nervous system. Even though such enteric nervous system endophenotypes are difficult to detect with current methodology, they may be reflected in alterations in motility and secretion.) Because homologous brain endophenotypes can be identified in rodents, they may be important for target identification and early stages of drug development ("target engagement or proximal biomarker").[3,15] It remains to be determined whether certain brain endophenotypes, which have a high correlation with a particular symptom (eg, abdominal pain), may even become relevant as surrogate endpoints in those FGID (eg, IBS, FD, noncardiac chest pain), where the severity and intensity of abdominal pain is the main determinant of symptom severity and health care utilization. Proof-of-concept studies with effect candidate drugs are required to test this hypothesis.

For the field of FGID research, where do these developments leave the traditional emphasis in the classification, treatment, and outcomes assessment on symptoms and patient-reported outcomes? It would seem that no matter how exciting and promising the new approaches are, until reliable biomarkers, reproducible endophenotypes, and related networks have been identified and validated, the field of neurogastroenterology will have to live for some time with the traditional, symptom-based approach to drug development. (Table 1).

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Table 1

Selected Group of Biomarker Candidates That May Qualify as Surrogate Endpoints for FGID[a]

Biological process	Pathologic process	Biomarker candidate	May qualify as surrogate endpoint for
Colonic transit	Slow transit, colonic inertia	Colonic transit measurement by scintigraphy, radiopaque markers, wireless capsule	Colonic inertia; IBS-C subset with slow colonic transit[2]
Gastric emptying	Delayed gastric emptying, gastroparesis	Gastric emptying measurement by scintigraphy, stable isotope breath test, wireless capsule	Diabetic gastroparesis; functional dyspepsia subset with delayed gastric emptying[7]
Visceral sensitivity	Visceral hypersensitivity[b]	Barostat distension of esophagus, stomach, colorectum	Insufficient data[16]
Brain structure and function	Regional grey matter changes,[b] altered brain networks[b]	Structural MRI scan of brain; resting state	Insufficient data
Mucosal immune system	Mucosal immune activation	Mast cell count/functional properties; mucosal cytokine expression	Not supported by published data
Signaling molecules	HPA axis dysregulation,[b] altered mucosal serotonin signaling; altered noradrenergic signaling[b]	Diagnostic panels; salivary cortisol levels; urinary 5-HIAA levels; urinary catecholamine levels	Not supported by published data
Luminal milieu	Dysbiosis; inflammatory markers	Stool proteases; stool calprotectin; intestinal flora (metagenomic sequencing)	Insufficient data
Small intestinal microbiota	Small intestinal bacterial overgrowth	Hydrogen breath tests	Bloating; insufficient data for IBS

FGID, functional gastrointestinal disorders; HIAA, 5-hydroxy indole acetic acid; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; HPA, hypothalamic—pituitary–adrenal; MRI, magnetic resonance imaging.

[a] Shown are a selection of candidates that have been discussed at a recent workshop.[6]

[b] Being evaluated as endophenotype candidates.