

Role of the Opportunity To Test Index in integrating diagnostics with therapeutics

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In theory, the introduction of a novel test to accompany a therapy should be simple and automatic. However, in reality, the marriage of a test with therapy will not be a simple one, since each industry operates with its own distinct business model. Of concern to the pharmaceutical industry is the potential commercial dependency of a drug on the performance and implementation of a diagnostic. These concerns are justified since the history of diagnostic tests is frequently one of under use. One of the factors cited by Rogers is the issue of how complex an innovation is to administer. Rogers demonstrates that an innovation that is difficult to administer will be implemented more slowly or be discontinued by the user group it was intended for. It is the author's view that understanding this micro interaction, experience and barriers of testing with the individual provider, in short the complexity of the test, will, in turn, provide those in the pharmaceutical industry with a methodology to consider their risk or exposure to a test upon which their therapy may become dependent in the US market. Since personalized medicine significantly marries the test and treatment decision, it is the perspective of the provider that will be paramount in determining which, if any, test is ordered and the subsequent clinical decision he or she is enabled to take upon the test response. Therefore, a focus of this perspective is to consider the issues of test implementation from the perspective of the US provider who will order and use the information they provide. The Opportunity To Test Index methodology is introduced, which the authors speculate may help quantify the level of risk a pharmaceutical company has to the complexity of a test upon which its therapy will be dependent. The methodology scores five key elements impacting test implementation: reimbursement, turnaround time, test administration, test interpretation and patient engagement.

There is an increasing amount of agreement on the vision for personalized medicine between regulators, pharmaceutical and diagnostic companies, and provider groups. Whilst there are only approximately 12 specialty therapies approved in the USA as of 2006 that would be described as targeted by some type of diagnostic (Table 1), a focus of investment by large and small pharmaceutical and biotech companies suggest that these are only the forerunners of a shift away from the 'one size fits all' model towards personalized medicine in primary care settings for some of the future therapies. For example, Sydney Taurel, Chief Executive Officer (CEO) of Eli Lilly (IN, USA) indicated that his company was making a significant investment in personalized medicine, and "exploring a new model of more tailored therapies." [101]. As recently as April 2005, Perlegen Sciences (CA, USA) made a significant investment licensing a peroxisome proliferator-activated receptor (PPAR) agonist from Mitsubishi

Pharma (Tokyo, Japan), which it aims to personalize with genomic tests for mainstream use in diabetes [102].

Although not all personalized medicines will require diagnostics, for example BiDil® (isosorbide dinitrate/hydralazine) is personalized to black Americans with heart disease, most targeted therapies are likely to depend upon new or existing diagnostic testing methods to ensure their uptake.

In theory, the introduction of a novel test to accompany a therapy should be simple and automatic: inform the provider the new test is available and is used to guide a specific therapy or therapies; and ensure the test can be supplied by a quality laboratory and fits within existing procedural and reimbursement codes. However, in reality, the marriage of test with therapy will not be simple, since each industry operates with its own distinct business model [1].

Of concern to the pharmaceutical industry is the potential commercial dependency of a drug on the performance and adoption of a diagnostic.

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Table 1. US personalized therapies/procedures.

Therapies	Test	Indication	Ref.
Trastuzumab (Herceptin®)	HER-2/neu receptor	Breast cancer: for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease	[101]
Antiretroviral drugs	TruGene®-HIV 1 Genotyping Kit	Guides selection of therapy based on genetic variations that make the HIV virus resistant to some antiretroviral drugs	
Cancer treatment regimens	Oncotype DX 21 gene assay	Detects mutations linked to the likelihood of breast cancer recurrence in women, and benefit from certain types of chemotherapy	
Irinotecan (Camptosar®)	UGT1A1	Colon cancer: variations in the <i>UGT1A1</i> gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects	[102]
Drugs metabolized by CYP	Amplichip® CYP2D6/ CYP2C19	US FDA classification 21 CFR 862.3360: This device is used as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information	[1]
Imatinib mesylate (Gleevec®)	BCR-abl	Chronic myelogenous leukemia: Imatinib mesylate is indicated for the treatment of patients with Philadelphia chromosome-positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon- α therapy	[103]
Imatinib mesylate	C-KIT	Gastrointestinal stromal tumor (GIST): Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors	[103]
Immunosuppressive drugs	AlloMap® gene profile	Monitors patient's immune response to heart transplant to guide immunosuppressive therapy	
Pharmaceutical and surgical prevention options and surveillance	BRCA1/2	Guides surveillance/preventive treatment based on susceptibility risk for breast and ovarian cancer	
Pharmaceutical and lifestyle prevention options	Familion® 5-gene profile	Guides prevention and drug selection for patients with inherited cardiac channelopathies such as long QT Syndrome, which can lead to cardiac rhythm abnormalities	
Pharmaceutical and surgical treatment options and surveillance	p16/CDKN2A	Guides surveillance/preventive treatment based on susceptibility risk for melanoma	
Mercaptopurine (Purinethol®)	TPMT	Guides adjustment of dose in treatment of acute lymphoblastic leukemia: Patients with inherited little or no thiopurine S-methyltransferase activity are at increased risk for severe Purinethol toxicity from conventional doses	[2]
Tamoxifen	Estrogen receptor	The estrogen and progesterone receptor values (in breast cancer patients) may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial	[3]

BCR-abl: Breakpoint cluster region Abelson; BRCA1/2: Breast cancer 1/2; CDKN2A: Cyclin dependent kinase 2a; CFR: Code of federal regulations; CYP: Cytochrome P450; HER2: Human epidermal growth factor receptor; TPMT: Thiopurine S-methyltransferase; UGT1A1: UDP glucuronosyltransferase 1 family, polypeptide A1; Source: Personalized Medicine Coalition.

These concerns are justified since the history of diagnostic tests is frequently one of under- and inappropriate use. Such underutilization is not, as is commonly believed confined to esoteric or rarely used tests, but applies also to mainstream tests targeted for use in primary care. For example, in one review of studies, rates of yearly urine checks in diabetics or 6-monthly hemoglobin

A1cs (HbA1cs) and creatinine kinase tests for hypertension [2], were requested less than a third of the time deemed clinically appropriate.

Rogers [3] and subsequent researchers [4] have described the many factors that influence implementation of novel medical technologies. Further studies report on the issue surrounding the diffusion of medical innovations in the USA,

and in particular that they are both complex and multifactorial [5]. One report presents several innovations and effective care practices that are low-cost and have gained relatively rapid regulatory approval and reimbursement coverage, but which have still been underused for years (e.g., diabetic eye exams, influenza and pneumococcal vaccinations among the elderly) [6].

Plek presents us with a useful framework for thinking about these complex issues [7]. The author indicates that we should consider three interacting processes, namely:

- A generation process that involves the creative thinking that leads to the birth of the innovation;
- An implementation process that involves the challenges associated with putting a concept into action and embedding it into the day-to-day routine;
- A widespread adoption process which involves those things that we do (or fail to do) that accelerate (or impede) the adoption of the new practices across to new users.

Processes of diagnostic innovation and their adoption/diffusion across organizations are dealt with adequately in the literature, the process of implementation of a specific test with an individual healthcare provider are not.

One of the factors cited by Rogers is the issue of how complex the innovation is to administer [3]. Rogers demonstrates that an innovation that is difficult to administer will be implemented more slowly or be discontinued by the user group it was intended for. Rogers and colleagues suggest that if a test is significantly burdensome to the provider, all the other influences are unlikely to matter.

It is the authors view that it is understanding this microinteraction, experience and barriers of testing with the individual provider, in short the complexity of the test, which will, in turn, provide those in the pharmaceutical industry with a methodology to consider their risk or exposure to a test upon which their therapy may become dependent in the US market. Although the same issues associated with test implementation in a clinic appear to be replicated in Europe [104], this paper speculates a method by which issues of diagnostic test implementation might be measured and understood in the US healthcare setting. Such measurement and understanding is particularly relevant to a pharmaceutical industry concerned about the dependence of its therapy upon a diagnostic test in its largest global

healthcare market. Most papers concerned with test use assess the impact on the laboratory, not the provider, therefore, a further focus of this perspective is to consider the issues of test implementation only from the perspective of the provider who will order and use the information they provide. Since personalized medicine significantly marries the test and treatment decision, it is the perspective of the provider that will be paramount in determining which test or if any is ordered and the subsequent clinical decision he/she is enabled to take upon the test response.

Opportunity To Test Index

The Opportunity To Test Index (OTTI) is a technique that I believe may be useful to forecast the level of complexity a novel test will be perceived to have when first introduced to a provider at launch. Since the aim of personalized medicine is to ensure that a provider will implement or order the test in a timely way to enable therapeutic choices, the index defines the level of receptiveness a provider will have to that test.

The concept of OTTI is simple. On a given day, what opportunity does the provider have to obtain and manage a seamless, trouble-free test answer. If he or she uses the test and obtains a seamless test outcome then the test index is 1– or perfect. The provider can then proceed to prescribe the targeted therapy. If an impediment to the test answer occurs that impedes easy patient management, then the Opportunity To Test Index is less than 1.

We can break this down further by considering which aspects of a test implementation create complexity in the first place and giving each of them a sub-level score. The following elements would appear to influence the provider's perception of the complexity of a new test.

Reimbursement

There is a general perception within the pharmaceutical industry that managed care acts as a gatekeeper to the introduction of novel technology. Several studies of innovations and diagnostics argues that the processes that result in regulatory decisions are relatively more fair and balanced than those supporting coverage and reimbursement, and that the latter is increasingly a deterrent to the diffusion of new technologies [8,9]. Ongoing research at the Robert Wood Foundation continues to explore how overall managed care policies limit the diffusion of medical technology [105].

When a diagnostic test is adequately reimbursed and covered, most are reimbursed by payers to the laboratory directly, thus removed from the

provider. Despite this, the provider is not immune to the degree to which a test has an incomplete reimbursement profile. The physician's office relationship begins with whether or not the patient's insurance covers the particular test in the first place. One study showed that, whilst over 80% of employers provided coverage in 2001 for wellness or gynecological exams, far fewer covered chlamydia screening or cholesterol tests [6]. This incomplete coverage has also impacted the Herceptest™ where Blue Cross and Blue Shield (BCBS) of Kansas (KS, USA) considers the Hercep test only medically necessary when the International Classification of Disease (ICD)-9 diagnosis code is in the region of 174 – malignant neoplasm of female breast – but Hercep test billed with a 183 assessment of ovarian cancer will be denied as not medically necessary, because ovarian cancer does not warrant the test. Whilst in these circumstances the patient may pay out of pocket, this is a move that will require a different billing process and added test administration.

It is unlikely that a participating lab will cease to offer a test if they are not fully reimbursed, particularly if it is an infrequently ordered test, but clearly their commercial interest in supporting providers with additional analysis or rapid turnaround times on loss-making tests will be low. In addition, new tests with new current procedure terminology (CPT) codes, which may more adequately reflect the cost of running the test, take time (12–18 months) to diffuse across the payers system and help frustrate test uptake in at least the first 12 months of test launch.

Turnaround time for the test

The turnaround time (TAT) for a test is a function of the degree of automation a given diagnostic test platform uses. For example, a test on a new enzyme-linked immunosorbent assay (ELISA) platform could probably be incorporated into existing test platforms and provide results from one of thousands of labs owned either by LabCorp or Quest across the USA within hours. A multiplex DNA test developed on a specialized platform and conducted in only one or two test sites may take up to 12–14 days to provide an answer. Clearly, if significant treatment choices are going to be made, a provider may be willing or forced to wait for the test answer. However, the wait will probably increase patient angst and the perception that the provider can do little to help other than delay starting treatment. Where test choices or the ability to prescribe without a test answer

exist, the provider is more likely to avoid test adoption for tests that have inconvenient turnaround times.

Interpretation of results

We often think of a test result as giving a provider an unequivocal choice, a clear yes or no to the presence of a given disease, or a number (e.g., total cholesterol, which is a measure of low-density lipoprotein [LDL] and high-density lipoprotein [HDL], over which treatment, for example, with statins is warranted). However, even on tests with significant commercial focus behind them, providers often find difficulty interpreting test results, as was the case in a study completed in Europe where between 16 and 20% of respondents consider the interpretation of human epidermal growth factor receptor 2 (HER2) results to be difficult [10]. We can see similar issues of adoption with HER2 testing in the USA, where well recognized interlaboratory variability of the immunohistochemistry (IHC) methodology, where providers received unacceptably different answers depending upon where the test was run, was also experienced when the more sensitive fluorescence *in situ* hybridization (FISH) testing method [106] was introduced (despite the increased accuracy of the FISH technology, only 35% of oncologists surveyed at the 19th Annual Breast Cancer Miami Conference were using the FISH test on their patients by 2002 [107]).

Studies have recognized this problem as one where the process of test self-certification under the College of American Pathology (CAP) has not led to consistent test standardization between laboratories even for the same test technique, making comparative assessment difficult [11]. The CAP is a privately run professional body with a central role in the oversight of pharmacogenetics testing services, although it is not strictly regarded as a regulatory body (laboratory four). Firstly, CAP has 'deemed status' and can thus undertake clinical laboratory improvement amendments certification inspections (see above). Secondly it runs its own CAP-accreditation scheme. Finally, CAP presides over a quality-assurance review system known as proficiency testing.

Providers can also find themselves with a number without any third party-endorsed guidelines, as, for example, with the recently launched AmpliChip CYP450 multiplex test that is not accompanied by treatment guidelines detailing which patients warrant different treatment decisions and which do not. This is not an easily fixed issue as it can take many years to develop

Table 2. Opportunity To Test Index states of complexity scoring.

OTTI burden score	Provider perception
0.0	The provider perceives the burden to be significant and preclusive
0.4	The provider perceives the burden to be repetitive requiring additional resource
1.0	The provider perceives no burden

OTTI: Opportunity To Test Index.

consensus-based guidelines guiding treatment choices from test results. One significant study of 1251 providers [12] across eight specialties showed the degree to which providers perceive they are ill-equipped for a new era of complex tests for their patients, with 25% of the providers indicating that genetic tests for cancer susceptibility have too many inaccurate or ambiguous results.

Patient engagement

Despite the availability of WHO and American Medical Association (AMA) guidelines on patient counseling, and areas of patient engagement – particularly in emotive diseases – in practice remains suboptimal. Often the decision to test a patient is more traumatic than the decision to treat a patient. This is increasingly true in areas of hereditary or infectious diseases where the impact on patients’ families or relationships is also a factor for consideration. The impact of a genital herpes diagnosis on a patient carries a significant stigma [108] and imposes equally significant burdens on providers. Patient consent and specific counseling tools may also be absent when a test is initially launched. Whilst this is unlikely to lead to a provider’s unwillingness to run a test, it does have implications for patient management. Such burdens led to the development of appropriate counseling tools for Huntington’s disease. However, such guidelines were several years in creation and validation. The need for additional patient engagement beyond the specific consultation may be acceptable when the provider has sufficient resources to cope with a 40–100-min patient counseling session, but a real barrier to test adoption when they do not. In the Freedman study across eight provider specialties, this issue was again researched, with 75% of providers perceiving that that clear guidelines are not available for

managing patients with positive test results. Only 29% of physicians reported feeling qualified to provide genetic counseling to their patients [12].

When a new therapy is launched we typically see an investment in CME programs, patient hot-lines and dedicated patient websites. This type of informational support is hitherto rare in the diagnostic realm, again placing informational burdens on the provider and, more importantly, the need to directly invest in additional in-house resources to handle these new patient management issues arising out of complex test answers.

Test administration

The degree of the providers’ back-office support for a test is considerable, from posting samples or arranging collection, to resolving reimbursement discrepancies and chasing test reports (particularly those which are not electronic or not tested in easily accessed laboratories), and requires trained and dedicated staff. As with the other aspects of test complexity, we are unlikely to see a provider refuse to run a test because of office administration issues alone, but they contribute to the burden of testing which increases with each new and novel testing technique. One study in particular highlights the issue of marrying the introduction of new information or services, for example, the fact that most electronic medical records (EMRs) do not, in general, include the data necessary to navigate practice guidelines [13]. This is despite the recognition that computer and internet-based information and data in support of diagnosis, medical decision making, and ordering have the potential to replace slow access to written documents and paper-based systems [4]. An additional problem is that the payer systems for reimbursing tests and therapy are two different systems, that currently do not communicate automatically with each other. The extent to

Table 3. Opportunity To Test Index scale applied to reimbursement.

OTTI burden	
0.0 (preclusive)	The new test is not covered by the patient’s insurance policy
0.4 (repetitive)	New CPT codes have been introduced but the payer or lab does not yet have them embedded on the system leading to test delays and administration issues.
1.0 (none)	No involvement in the test billing is required

CPT: Current procedure terminology; OTTI: Opportunity To Test Index.

Table 4. Opportunity To Test Index scale applied to turnaround time.

OTTI burden	Turnaround time
0.0 (preclusive)	The turnaround time for the test is several weeks, which itself falls outside the timeframe a provider needs to make a decision about the particular therapy
0.4 (repetitive)	There is no consistent pattern to the turnaround time for the test, administrative burden increases, and frustrating the provider's ability to give patient expectations or manage repeats visits
1.0 (none)	The turnaround time of the test fits seamlessly into the clinical timeframe required for deciding on this particular therapy

OTTI: Opportunity To Test Index.

which this will present a barrier to the administration of tests or place additional onus on clinics to identify where a particular test is connected with a particular therapy is, as yet, unknown.

Measurement of the Opportunity To Test Index

Given the onus to provide patients with optimal healthcare, an imperfect situation with any one of these implementation complexity elements alone is unlikely to lead to test avoidance or discontinuation. However, where the burden of complexity increases, there is likely to be a point where the test remains unused or is discontinued after a small number of patients. The widespread levels of test underutilization support this contention [2]. The OTTI measurement scale is suggested as a method to measure and model the perceived accumulation of complexity and speculate a cut-off point beneath which test avoidance is more, rather than less, likely as provider behavior.

On our OTTI scale there are three possible states of complexity burden that impact the Opportunity To Test Index as described in Table 2.

As an example we might apply this to the five elements of complexity factor. By simply applying a scoring to each of the complexity factors and averaging the totals, we can model the cumulative impact of all the complexity factors at work (Tables 3–7). On our OTTI scorecard we have presented and described four possible scenarios (OTTI score is calculated by averaging the five subscores) (Table 8).

- Scenario A: OTTI score = 1. The test is perceived by the provider to be a routine part of his patient management, requiring no additional resource and providing an automatic and timely test answer enabling appropriate treatment;
- Scenario B: OTTI score = 0.76. The test is perceived by the provider as having a number of shortcomings typical of a newly introduced test. In this example, new CPT codes have been introduced but the payer or laboratory does not yet have them embedded on the system, leading to test delays and the need for the office manager to intervene consistently to sort this out. On top of this, the turnaround time for the test is 14 days – typical of new molecular tests; however, the patient is eager to commence therapy and the provider is unwilling to wait any longer before making a treatment choice. Other aspects of the test are perceived to be trouble free. In this scenario we speculate that the provider is likely to absorb the burdens of the test and continue ordering the test with reservations;
- Scenario C: OTTI score = 0.64. In addition to the burdens perceived under scenario B, the provider is faced with the fact that sample collection and transportation to a specialized laboratory across the country soaks up the time of his/her nurse practitioner or laboratory technician, preventing other work from being completed and adding overheads to the clinic. In this scenario the provider is likely to

Table 5. Opportunity To Test Index scale applied to interpretation of results.

OTTI burden	
0.0 (preclusive)	The provider perceives the results to be inconsistent between laboratories insufficient for him/her to have confidence in the result from either.
0.4 (repetitive)	The test result has a history of interlaboratory variability in addition to which the test is not significantly unequivocal to aid the clinical diagnosis.
1.0 (none)	The result is unequivocal

OTTI: Opportunity To Test Index.

Table 6. Opportunity To Test Index scale applied to patient engagement.

OTTI burden	
0.0 (preclusive)	The new test adds significant counseling or education resource burden to the provider which he/she is ill equipped to deal with resulting in the perception that he/she cannot manage the patient properly
0.4 (repetitive)	The new test triggers a regular need to counsel or educate patients and although the provider has the tools to do this, he/she perceives that the clinical outcome can be better managed without the test
1.0 (none)	The test is a benefit to patient engagement

OTTI: Opportunity To Test Index.

consider alternatives to doing the test or making his or her treatment choice on other empirical clinical evidence;

- Scenario D: OTTI Score = 0.36. In addition to the burdens perceived under scenarios C and D the provider is faced with difficulty understanding what the results are telling him/her. The provider already perceived this to be an awkward test, the patient is being asked to pay for the test or payers consulted prior to the test use and the turn around time for the test falls far outside the ability of the recommended therapeutic treatment window. In this instance the provider is likely to discontinue using the test after only two or three patients.

The tipping point

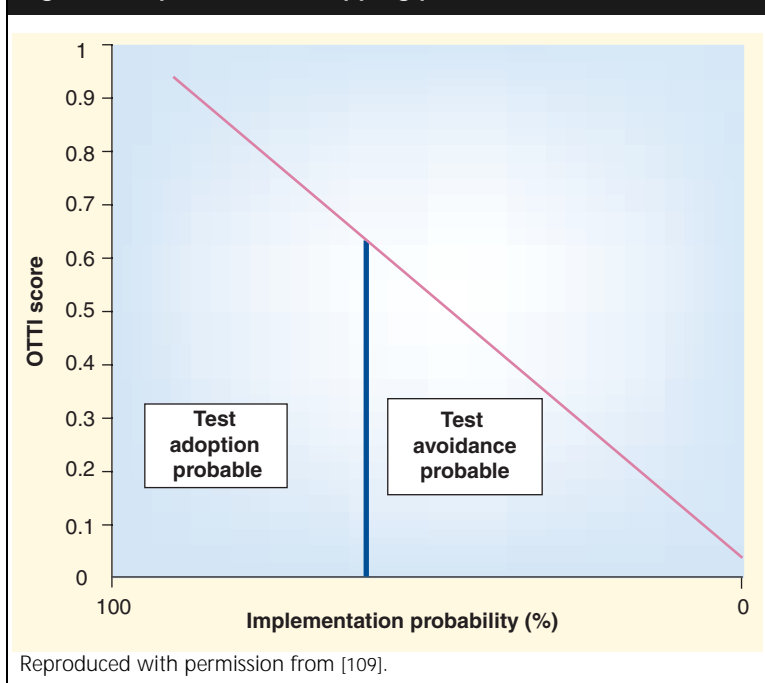
The concept of a tipping point for innovation implementation has been explored in the context

of healthcare in several studies [4,14]. By its nature it is an arbitrary point at which we try to define if the majority of providers will behave in a consistent way, either to implement consistently a test or avoid or discontinue its use.

As Figure 1 in our OTTI scoring we speculate that an inclination towards test avoidance or discontinuation begins at a point where the OTTI score drops beneath 0.64. This tipping point level has been identified in three ways:

- All the possible scoring combinations have been calculated and independently assessed by three experts in diagnostic test diffusion as to where the tipping point is likely to lie based on the qualitative scenarios they forecast;
- To further validate this level the scoring has been compared retrospectively to the known annual provider implementation rates of five representative novel benchmark diagnostic tests: B-type natriuretic peptide (BNP), HER2, Troponin, lipoprotein associated phospholipase A2 (LpPLA2) and C-Kit;
- Finally, the authors have initiated a research program to validate provider choices in focus groups by describing all the possible scenarios and recording and scoring the choices. The research will also aim to define if there are measurable trade-offs, which could help give a relative weighting score to the elements chosen. This work will be completed in late 2007.

Figure 1. Implementation tipping point.



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How might the Opportunity To Test Index be used?

For the purposes of modeling, the definition of a tipping point does help forecast a probability that a novel test will be perceived by most providers in a certain way, either enabling a higher or lower probability of its implementation. For the pharmaceutical industry, understanding and measuring this level of risk is critical in areas where a therapy is dependent upon the implementation of an individual test. Some pharmaceutical planners

Table 7. Opportunity To Test Index scale applied to t-test administration.

OTTI burden	T-test administration
0.0 (preclusive)	New test is not embedded in regular office systems
0.4 (repetitive)	New test triggers consistent office management issues that cannot be solved without undue resources
1.0 (none)	Test administration is seamless

OTTI: Opportunity To Test Index.

are assuming therapy prescribing anyway, where a companion test has been difficult to run. This author believes this to be a high-risk assumption and a tacit acceptance that the test has a very low OTTI score. More importantly, modeling future probable responses in turn identifies actions which taken today may change the future tipping point, making the implementation issues of the test less risky for the pharmaceutical company. Where a therapy is dependent upon a test, the ideal OTTI score is obviously 1.0 since that removes any impediment of test complexity to Rx prescribing. In order to engineer such a score it is essential to address the shortcomings within each of the five elements identified as contributing to complexity. For example, to turn scenario C above (where test avoidance is possible) to scenario B (where test implementation is likely) might require an investment to move a test from one central molecular testing laboratory, instead creating a standardized (i.e., consistent) test available in 6–10 major reference laboratories across the country. Validating this test transfer could take up to 6–12 months in advance of the therapy launch.

Therefore, in real terms, OTTI can help identify what work needs to be done in the period before a test launch, in order to create a high OTTI score. The work essential to be completed should be dictated by how far up the OTTI score pharma marketers perceive they need to be in order to ensure their therapy has a viable market and is not constrained by the nonimplementation or discontinuation of a novel test. Test sellers are unlikely to be able to create OTTI scores of 1 for novel tests, upon test launch, and this tool allows

us to consider situations, which, whilst far from perfect, are unlikely to be a barrier to widespread test implementation and thus therapy prescribing. For a pharmaceutical industry unfamiliar with the nuances of the diagnostic market, OTTI aims to enable better planning and removal of potential risks to the implementation of a personalized medicine solution.

The author accepts that complexity of a test is only one of the many factors cited by Rogers and colleagues, contributing to behavior change, favoring or avoiding innovation implementation. Nonetheless, given the dependence of a therapy on a test response implicit in the new era of personalized medicine, it is a critical one. The author aims to bring into focus a detail of the diagnostic market which so often leads to underutilization despite widespread awareness of a tests benefit. A detail if you like within which, for personalized medicine at least, the devil clearly lurks.

Outlook

The pharmaceutical industry is beginning to consider the complexities of test adoption and its impact on the success of personalized medicine tomorrow. Pharma will embrace diagnostic planning as a new competency in targeted therapy planning. This competency will seek to build processes, techniques and systems to remove impediments to test adoption and remove the uncertainties associated with diagnostic diffusion today. Techniques such as OTTI, once validated, may be commonplace in everyday pharma parlance as we formalize and rebuild the bridges between the worlds of therapy and diagnostics.

Table 8. Opportunity To Test Index scorecard.

OTTI scorecard	Scenario A	Scenario B	Scenario C	Scenario D
Reimbursement/billing	1	0.4	0.4	0
Test turnaround time before prescribing	1	0.4	0.4	0
Test administration	1	1	0.4	0.4
Interpretation of result	1	1	1	0.4
Patient engagement	1	1	1	1
OTTI score	1	0.76	0.64	0.36

OTTI: Opportunity To Test Index.

Highlights

- The implementation of personalized medicine is in turn partly dependent upon the implementation of novel diagnostic tests into mainstream use.
- The Opportunity To Test Index (OTTI) is a technique used to forecast the level of complexity a novel test will be perceived by a provider to have at launch. The OTTI measurement scale suggests a cut off beneath which test avoidance is more likely.
- Any one of the complexity factors alone is unlikely to lead to test avoidance or discontinuation, but where the burden of complexity increases, there is a point where the test remains unused or is discontinued after a small number of patients.
- Modeling the likely future OTTI score of a novel test will allow pharmaceutical planners to determine specific changes to which the diagnostic market development and preparation are required to ensure a viable and efficient test environment upon which their therapy will be dependent.
- Research to further validate the OTTI scale is underway.

Bibliography

1. Keeling P: Fear of Theranostics. *Decision Resources* November (2005).
 2. The Lewin Group: The Value of Diagnostics Innovation, Adoption and Diffusion into Health Care (2005).
 3. Rogers E: *Diffusion of Innovations. 5th edition*. Free Press, NY, USA (2003).
 4. Coye MJ, Aubry WM, Yu W: The Tipping Point and Healthcare Innovations. *Proceedings of the NIHMF Conference*, Washington DC, USA, November 2003.
 5. Plsek P: Complexity and the Adoption of Innovation. *Proceedings of the Strategies to Speed the Diffusion of Evidence-Based Innovations Conference*, Washington DC, USA, January 27–28, 2003.
 6. The National Institute for Health Care Management. *Proceedings of the NIHCM Accelerating Improvement in Healthcare (NIHCM) Research and Education Conference*, Washington, DC, USA, January 27–28, 2003.
 7. Plsek P: Complexity and the Adoption of Innovation. *Proceedings of the Strategies to Speed the Diffusion of Evidence-Based Innovations Conference*, Washington DC, USA, January 27–28, 2003.
 8. McGivney WT, Hendee WR: Regulation, coverage, and reimbursement of medical technologies. *Int. J. Radiat. Oncol. Biol. Phys.* 18(3), 697–700 (1990).
 9. Steiner CA, Powe NR, Anderson GF, Das A: The review process used by US health care plans to evaluate new medical technology for coverage. *J. Gen. Intern. Med.* 11(5), 294–302 (1996).
 10. Woelderink A, Ibarreta D, Hopkins MM, Rodriguez-Cerezo E: The current clinical practice of pharmacogenetic testing in Europe: TPMT and HER2 as case studies. *Pharmacogenomics J.* 6(1), 3–7 (2006).
 11. Anon: Trastuzumab plus chemotherapy improves survival in early-stage HER2-positive breast cancer patients. *Oncology (Williston Park)* 19(7), 851, 862 (2005).
 12. Freedman AN, Wideroff L, Olson L *et al.*: US physicians' attitudes toward genetic testing for cancer susceptibility. *Am. J. Med. Genet.* 120A(1), 63–71 (2003).
 13. Tierney WM: Improving clinical decisions and outcomes with information: a review. *Int. J. Med. Inform.* 62(1), 1–9 (2001).
 14. Gladwell M: *The Tipping Point: How Little Things Can Make a Big Difference*. Little, Brown and Company, MA, USA (2000).
- Websites
101. Kaiser Family Foundation. Conversations on Health With Sidney Taurel May 10, 2006. www.phrma.org/about_phrma/ceo_voices/kaiser_conversations_on_health_with_sidney_taurer
 102. Perlegen Sciences. News Release: Companies Usher in New Era of Personalized Medicines in Metabolic Disease. April 12, 2005. www.perlegen.com/newsroom/pr/2005/2005_04_12_MCC-555_Joint_Press_Release.pdf
 103. Personalized Medicine Coalition. Collins Presentation www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf
 104. Zika E *et al.*: Pharmacogenetics and Pharmacogenomics: State-of-the-art and potential socio-economic impacts in the EU (2006). http://esto.jrc.es/detailshort.cfm?ID_report=1387
 105. Baker LC: Managed Care Policies Limit the Diffusion of Medical Technology. www.rwjf.org/reports/grr/028072.htm#int_grantinfo
 106. LabCorp. Check W CAP Today, February 2002. www.labcorp.com/clinicaltrials/what/HER2.pdf
 107. 19th Miami Breast Cancer Conference, Controversies in breast cancer Section 12. www.breastcancerupdate.com/miamiconference2002/bc12.htm
 108. American Social Health Association website, Herpes resource Center. www.ashstd.org/herpes/herpes_emotional.cfm
 109. Diaceutics website. www.diaceutics.com