A NEW DISEASE LEVEL PRECISION MEDICINE MODEL; STARTING WITH MELANOMA

by Peter Keeling and Jeff Waldron

In just a few months, the PM Connective expects to complete a new model for melanoma that will offer clinical and financial benefits in precision healthcare. Early indicators suggest the model will provide substantial improvements in health outcomes and lower overall healthcare costs by shifting the entire management of melanoma from the expense of treating late stage disease to earlier interventions when, significantly, this aggressive condition is curable. But just how robust is the model? To understand the strength of this innovative tool it is important to look at the nature of the disease, and how the model was developed.

Managing melanoma better

The PM Connective chose to design its model first in melanoma. The importance of a valuation model in melanoma is that the condition can be cured if found and treated in the early stages when it affects only the skin. Unfortunately, this is currently not the case for a number of patients.

Melanoma is one of the least common forms of skin cancer, but it is one of the most aggressive, because of its potential to spread to other parts of the body. Almost one million Americans live with this condition, and rates are rising, especially among children and teenagers. But while the disease accounts for around 1% of skin cancers diagnosed in the USA, it causes most of the skin cancer deaths.

Data on patient distribution by disease stage indicates that more than 235,000 Americans have Stage 0-I of the disease (when the tumours are still on the skin), and 30,000 are living with more advanced melanoma where the tumours have metastasized to other parts of the body (Stages III and IV). Yet while around $2,600 million a year is spent treating the two early stages, when a cure is still possible, a significant $6,800 million is spent treating Stages III-IV. Clearly, if more people were diagnosed and treated with first line therapies sooner it could have a huge impact on their clinical outcomes.

Historical cost data suggest that more effective deployment of diagnostics and therapies could reduce deaths from metastatic melanoma in the USA by between 21% and 71%. This premise is substantiated by early indications from the PM Connective’s model for melanoma, which suggests that early interventions could indeed save patients’ lives.

“There needed to be an organisation that could look at the value of precision medicine and demonstrate how it could transform people’s lives now, with existing or near market technologies and education at the micro level,” says Peter Keeling, CEO of Diaceutics, which founded and sponsors the Connective. A small task force, led by Keeling, was therefore set up to find the terms of reference for this organisation, and at the end of six months Diaceutics established the not-for-profit PM Connective with the goal of seeing what changes could be identified to help...
articulate and extract the full value of precision medicine within melanoma. The vision to better integrate currently available or near market technologies into each healthcare stakeholder’s process, gave inspiration to the name Connective itself.

**Grass roots knowledge bank**
The PM Connective is now a collaborative network of around 160 key representatives from all healthcare stakeholders, or ‘silos’. This level of experience, expertise and integration means the Connective is essentially a grass roots knowledge bank for the complexities of dealing with this disease, its technologies, treatments and costs.

Moreover, by creating a collaborative network the Connective has ensured each silo has an understanding of the perspective and issues faced by each of the other silos, and that together they could build a model that provides value and benefits to each individual silo. Importantly, targeting the model at the disease-specific level further ensures it is focused and its recommendations can be readily implemented.

To date, the Connective has held two workshops to convene all healthcare silos for an integrated conversation instead of one-on-one discussions. These workshops, which looked at the disease holistically, were held in April and December 2016, at Rutgers Cancer Institute of New Jersey, an early supporter of the Connective under the guidance of Dr. Howard Kaufman, the Institute’s Associate Clinical Director and Chief Surgical Officer. Prior to each workshop a detailed survey was sent to each collaborator to garner their ideas, and to broaden their reach if some of them couldn’t make it on the day.

The first workshop focused on establishing the hurdles to implementation of precision medicine – which the collaborators whittled down to six critical high-level issues. Information from the two surveys, and the first workshop, was then distilled and synthesised in preparation for the second workshop, where the collaborative network developed a broad range of potential precision medicine solutions. These are currently being fully defined, examined and processed through the valuation model to quantify and prioritise interventions for implementation. The solutions have been sorted by topical areas and each has been prioritised (A, B or C) and given an estimated timing (near term, medium term, or long term).

In summary, these solutions are:

- **Clinical practice and operational**
  - Improved clinical collaboration (priority A – near term).

Melanoma is usually diagnosed and treated at a local level, usually a community hospital, and if the disease progresses the patient is often transferred to a regional facility such as a specialist cancer centre. Generally, these transfers do not include full transmittal of early diagnostic and/or therapeutic results, such as tumour samples, resulting in either delayed response by the specialised facility or the need to take new tumour samples and biopsies. The reason for this, in part, is because the local hospital does not receive additional reimbursement for providing data or samples to the speciality facility. At a more general level, a precision medicine approach requires full collaboration between providers, possibly with reimbursement tools to encourage the process.
Melanoma risk characterisation (priority A – medium term).
Initially, patients often present with Stage I or II melanoma. Some will respond positively to early treatments and may exhibit no-evidence-of-disease, while others may progress to the metastatic phase. If there were substantiated diagnostic assays to better predict risk characterisation, treatments given in the early stages of melanoma could be segmented to provide more aggressive targeted therapy and/or earlier adjuvant therapy to patients most likely to benefit. This involves a combination of prognosis and predictive elements. Prognosis is the risk characterization part, which provides information on who is more or less likely to relapse. Predictive assays can tell you if a patient is likely to respond to a specific therapy or not. Integration of both aspects is difficult, but offers the most potential for improved outcomes.

New options for melanoma adjuvant therapy (priority A – medium term).
More adjuvant therapy options are needed. For example, early identification and treatment of breast cancer patients using the HER 2 biomarker and Herceptin improved outcomes, but it wasn’t until Herceptin was used as an adjuvant therapy in qualified patients that vast improvements in breast cancer outcomes were seen.

Immunotherapy’s emergence as 1st-line treatment displaces traditional targeted therapy (priority A – near term).
Sequence and timing of both targeted therapy and immunotherapy needs to be better defined. Providers are increasingly using immunotherapy as a 1st-line treatment for melanoma but if a patient doesn’t respond this poses difficult decisions about when to switch to more traditional targeted therapy. Complications occur involving both ‘pseudo-response’ to immunotherapy that doesn’t last, and where targeted therapy may be less effective in later stages than earlier ones. The key challenge is to find a way to better stratify/identify patients who are most likely to respond to immunotherapy so they are treated with that first, whereas those less likely to respond are provided with targeted therapy or other treatments first.
● Consideration of clinical trials as standard-of-care for select patients (priority A – near term).

Rapid development of novel therapies, including combination therapies, has led to clinical trials becoming de facto standard-of-care for patients, particularly with metastatic disease. At the Rutgers Cancer Institute roughly 60% of metastatic melanoma patients are part of clinical trial therapies. This is easier at centres of excellence with associated medical schools like Rutgers, but needs to be promulgated more widely.

● Improvements needed in transition from pre-clinical to clinical trial process (priority B – longer-term).

Greater collaboration and integration of the pre-clinical research stage with the clinical trial process has the potential to ensure the most attractive research topics and targets get funded and orchestrated through both processes.

Diagnostics

● BRAF testing for melanoma is a critical determination but often occurs later in the patient pathway (priority A – near term).

BRAF gene mutation is the most common oncogenic driver mutation of metastatic melanoma. Treatment with BRAF and MEK inhibitors can result in a high tumour response rate and improve the survival of patients with BRAF V600 mutation. An analysis presented at the 2015 European Cancer Congress showed the estimated two-year overall survival rate with dabrafenib/trametinib was 51%. Treatment guidelines and standard-of-care need to be re-examined to determine the optimal timing of NARAF testing.

● Next generation sequencing (NGS) will become an essential diagnostic tool but is yet to be proven (priority A – medium term).

NGS is likely to become essential for diagnostics in melanoma, particularly for risk characterisation. An industry-wide focus on the clinical utility of NGS will hopefully drive validation and acceptance.

● Liquid biopsies can be effective tools but lack validation and costs can be high (priority B – medium term).

Liquid biopsies can be effective in risk characterisation, determining tumour burden and therapeutic drug monitoring to better measure patient response. However, lack of validation of performance and cost considerations currently limit their usefulness. An industry-wide focus would help.

● Innovation in diagnostics is held back by lack of incentives (priority B – longer term).

Reimbursement difficulties and lack of patent protection means the diagnostics industry has a challenging path to innovation. Payers will need to examine reimbursement of FDA-approved and laboratory developed tests (LDTs) diagnostics to encourage innovation of critical assays that help determine the use of extremely costly new therapies. One approach would be to create some form of incentive system for diagnostics firms similar to that used by the US Department of Defense for its vendors. It specifies “advanced market commitments” (incentives) for the development of new products or services.

● Diagnostic tests have differing effectiveness with little standardisation (priority B – longer term).

Lack of standardisation for diagnostics implies varying degrees of effectiveness by a given laboratory. Most assays are not FDA-approved and can often be (LDTs), resulting in confusion in the marketplace and lack of value for approved and validated testing. The worlds of FDA versus CLIA testing certification remain a challenge for providers.

Pharmaceuticals

● Adverse clinical and cost consequences of ‘step-edit’ or ‘fail first’ policies (priority B – longer term).

Policies dictate patients must first demonstrate lack of results on existing treatment options before being approved for new and often costlier therapies. Most new therapies get approved in metastatic patients for later lines of therapy. It is the fastest way to get to market and begin generating revenue to fund the follow-on studies to move the drug to earlier stages and earlier lines of therapy. Thus, more data is needed to support better first-line treatment such as anti-PD-1 immunotherapies.

● Benefits of combination therapy versus monotherapy are difficult to measure (priority B – longer term).

Many metastatic melanoma patients respond well to treatment using combination therapies, but options are difficult to determine and guidelines are lacking on standard-of-care. In addition to developing new drugs, there is a need for improved evaluation of the benefits and sequence of combination drugs, both as primary and adjuvant therapies.

Reimbursement

Lack of reimbursement for new diagnostic technology is often an obstacle to clinical interventions (priority A – near term).

Tumour-based NGS testing, liquid biopsies, and panels of tests for multiple biomarkers all face intense scrutiny from payers regarding efficacy and cost effectiveness. As more therapies become available, diagnostics that prove effective in determining which patients are most likely to benefit from them will gain more reimbursement. Concerted cross-silo industry effort is required to accelerate this process.

● Undetermined impact of new healthcare payment models alters reimbursement (priority B – longer term).

In the USA, innovations such as Accountable Care Organizations (ACOs) versus historical fee-for-service payment mechanisms pose a significant challenge to the healthcare system. Capping reimbursement to providers would dramatically change reimbursement decisions and guidelines. Thus, payers may not be the only decision-making stakeholder in the reimbursement process.

● Lack of transparency for the quality and cost of healthcare options and decisions (priority B – longer term).

Patients are being asked to assume much greater roles in selecting and paying for diagnostics and therapies for their medical conditions, but the industry is unable to offer the proper tools to allow them to make informed decisions. The solution will eventually be tools that indicate the pros and cons of therapeutic options along with measures of quality and cost of care by prospective providers.
Therapies in the late stage pipeline are linked to BRAFT status, but also to PD-L1 expression, NRAS, c-Kit and other biomarkers.
Regulatory

- Mismatch of regulatory approval processes with pace of diagnostic and therapeutic innovation (priority B – longer term).
  Regulators are struggling to keep pace with the rapid development of, and clinical trials for, a vast array of new diagnostic and therapeutic options, including companion and/or complementary testing.

Guidelines and education

- Clinical guidelines are inconsistent, often out of touch with the latest tests and therapies and not backed by hard evidence (priority B – medium term).
  Cancer centres of excellence, like Rutgers, are leading the charge in clinical practice, but guidelines and education will be critical in reaching all provider organisations and instilling consistency driven by verifiable and replicable health outcomes.

- Continuing education and public communications on melanoma causes (priority A – near term).
  Melanoma is increasing in younger people but some therapies are unsuitable for younger age groups. For example, young women with metastatic melanoma may not be good candidates for immunotherapy if it could also damage reproductive organs. Similar to breast cancer awareness, much greater public education and awareness will help drive prevention, as well as earlier diagnosis and treatment.

Identifying the benefits

At the third workshop, due to take place before the end of 2017, collaborators will be challenged with valuing each of these potential changes and identifying not only the benefit across all silos, but also the benefits within each silo. The workshops and collaboration have confirmed that most barriers can be identified and, for many of the key ones, solutions are nearer at hand than previously anticipated. It is the incentive to change which is missing.

Broadly, it is assumed these changes will involve accelerated disease interventions for both diagnostics and therapies; enhanced clinical investigation; faster regulatory payer input, review and approval, including reimbursement; improved education of providers and patients along with better access by patients; and reduced duplication between healthcare silos. By articulating the financial and clinical value which the change will unlock it is intended to enable a better dialogue between the silos and the articulation of different incentives and collaborative agreements.

With many of the components of radical disease level impact already available, and with the number of precision medicine therapies in melanoma likely to triple in the next five to ten years, patients deserve access to innovative treatments that can significantly improve their health outcome. This melanoma model, and the ensuing valuation framework, should provide each healthcare silo with a sound economic argument for utilising precision medicine. As Jeff Waldron, Executive Director of the PM Connective says, on this basis “it would be hard for an individual silo to say no”.

Peter Keeling has driven Diaceutics to become a leader in innovative solutions that enable pharma to leverage diagnostic testing globally. With over 30 years in international healthcare, Peter is a thought leader in diagnostic commercialization, a respected speaker at precision medicine events and has published widely. Peter has also spent extended periods in applied industrial research, including a year with MIT’s Pharmaceutical Program.

Jeff Waldron, Executive Director of PM Connective, is tasked with building and sustaining the network of collaborators. He has created greater awareness of the project through attendance at industry conferences – including the invitation-only, ninth Annual Scientific Retreat, organised by the Melanoma Research Alliance in February this year, which is so well connected to advocacy groups – and through round table discussions, including his joint presentation with Dr. Katherine Johansen Taber of the American Medical Association, on barriers to the adoption of precision medicine, at the Journal of Precision Medicine Leaders’ Summit in August last year.