Initiative Overview

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
BREAST CANCER WORKING GROUP

MARCH 2010

Improving Health Outcomes in Breast Cancer: Recommendations of the Breast Cancer Working Group

Breast Cancer: clear issues in unmet need, access and cost

Cancer Research UK notes, "Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for a tenth of all new cancers and 23% of all female cancer cases."[1] Around 429,900 new cases of breast cancer occur each year in Europe and an estimated 184,450 in the United States.[2,3] The lowest European rates are in eastern and southern Europe and the highest are in northern and western Europe. In Europe an estimated 132,000 people will die of breast cancer. Stella Kyriakides, past president of Europa Donna, highlighted the urgency of addressing this disease, "Within the European Union, every 2.5 minutes a woman is diagnosed with breast cancer. Every 7.5 minutes a woman dies from the disease." [4]

For all its unfortunate familiarity, all acknowledge that there are too few, effective courses of treatment for patients facing this life threatening disease. The complexity of the science underlying breast cancer tumour development and progression, i.e. the unique heterogeneity of each tumour, complicates the treatment regime as well as development of specific medicines for affected individuals.

Given the general high cost of treatment regimes for breast cancer, all also recognise the issues of access and burden of cost of breast cancer treatments to healthcare systems working within limited budgets. The broader media has particularly focused attention on the themes of value and sustainability in healthcare, as illustrated by one headline in the 2 July 2009 *Wall Street Journal*: *"Cost-effectiveness of Cancer drugs is Questioned."* The article quotes a recent National Cancer Institute study[5] in which "the widespread use of expensive cancer drugs to prolong patients' lives by just weeks or months was called into question." These pressures are particularly amplified in the current environment with the strong economic pressures and potential budgetary cuts that face European member states across all ministries and functions.

Challenges to progress in enhancing health outcomes in breast cancer

"We are at an important moment in cancer research, and being here together is critical to writing a new chapter on the way we all work together. We cannot continue to work in the way we have in the past in terms of drug development, as the science is pushing us to do something in a completely different way."

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[1] Cancer Research UK, "Breast cancer – UK incidence statistics.

[2] J. Ferlay, P. Autier, M. Boniol, M. Heanue, M. Colombet, P. Boyle. Estimates of the cancer incidence and mortality in Europe in 2006 Ann Oncol. 2007 Mar;18(3):581-92.

[3] American Cancer Society, *Cancer Facts and Figures 2008* (Atlanta: American Cancer Society, 2008), page 4

[4] No More Breast Cancer Campaign, "Breast Cancer: Europe."Quoted to Sue Claridge, in 'The Beacon'(Breast Cancer Network Australia's magazine) Issue 29, Summer 2004, p10.

[5] Tito Fojo and Christine Grady, "How Much Is Life Worth: Cetuximab, Non–Small Cell Lung Cancer, and the $440 Billion Question." Journal of the National Cancer Institute Advance Access, June 29, 2009, Available at: http://jnci.oxfordjournals.org/cgi/content/abstract/djp177

Issues that require robust and transparent discussions to support better outcomes in breast cancer include:

- **Aligning views of unmet needs and shared value definitions across stakeholders.** A regulator participant asked: *"Can we get an earlier sense of where are the areas of unmet clinical need from the clinician, payer and patient perspectives, and what the payers will pay for?"* As a payer-adviser stated, *"indiscriminate drug development occurs because the payers are not sufficiently signalling clearly enough and making sure that signal gets down far enough into the pharmaceutical company to provide the appropriate incentives."* A patient advocate emphasised how *"important it is that patients are involved in the earliest stages of development"* as well.
- **Defining regulatory and reimbursement processes for innovative drug development programmes**, for example that use novel combinations (i.e. combinations of new molecular entities) or involve targeted populations. This would include defining the standard of care, as well as the appropriate sub-population for clinical trials and the evidence requirements for accompanying diagnostics and appropriate incentives to support diagnostic development. One consistent theme heard in the challenges in developing new breast cancer medicines is the optimal path to defining standard of care particularly given the rapid pace of oncology science combined with the variable treatment paradigms that exist: *"how does one evaluate standard of care in an area that is evolving like breast cancer where clinical guidelines are unclear and where different treatment centres can use different approaches to care even if they are in the same region?"* The technical challenges in a field where the treatment paradigm shifts rapidly, presents issues when faced with timing and data gathering requirements for traditional randomised clinical trials: *"When starting the development of a new breast cancer medicine, most agree on the standard of care. But with so much going on in the cancer field, by the time you finish clinical trials 5–10 years later, the perception of what standard of care is has moved on and your results might look much less compelling."*
- **Defining the quality of life (QoL) measures and collection design requirements**, particularly given the lack of consensus in the field on QoL measures, and understanding to what extent QoL should be relevant in relation to given indications of efficacy, toxicity and tolerability in a drug profile. *"We all feel that supporting quality of life improvement is important, especially in the domain of cancer. But most cancer treatments result in a very poor quality of life. For this reason we tend to focus more on level of toxicity – not because it is less important but just because we do not have the right tools for measuring quality of life."*

Addressing the need for innovation in Breast Cancer treatment

Given the challenges stated above, breast cancer was a clear target area for a disease-specific working group convened by the European Healthcare Innovation Leadership Network. The Network is a public-private partnership initiative established by Tapestry Networks in 2006 that brings together a premier group of healthcare leaders from EU Member States who are

committed to collaboratively addressing the complementary goals of improving patient health outcomes as well as the climate for innovation within the constraints of pressures to control healthcare costs (attached in Appendix A is a list of members of The Network and in Appendix B, a list of participants of the Breast Cancer Working Group for reference). Working with governments, payers, patient advocates, regulators and industry the Network believes that the current model for bringing new medicines to market is unsustainable. They have identified the importance of a shared framework for measuring value if shared goals of ensuring access to innovative medicines and controlling healthcare costs are to be achieved. Network members recognised that moving the value discussion from the realm of abstraction to tangible, practical outcomes required a disease-specific focus (Breast Cancer and Type 2 Diabetes were chosen as initial focus areas for challenges both clearly bring to member state healthcare systems).

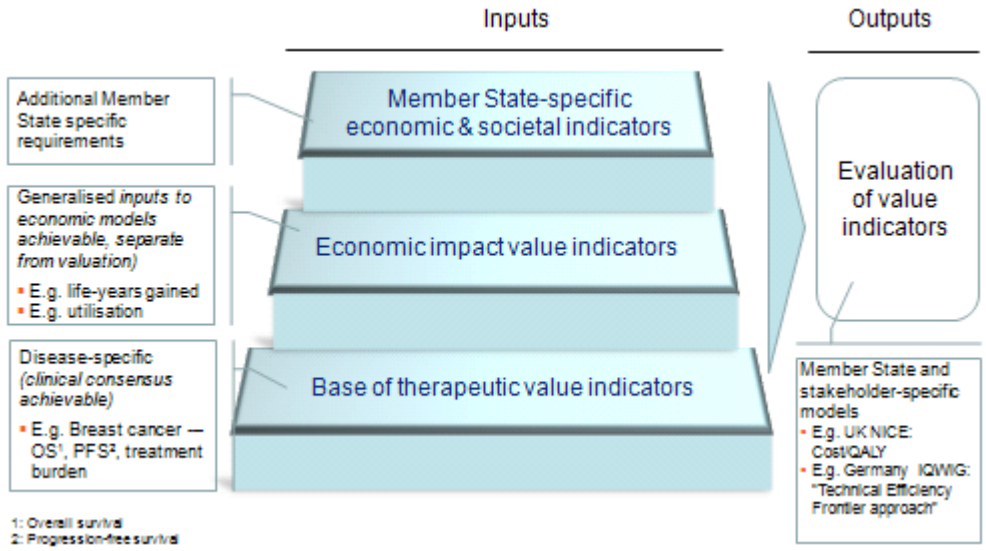
Over the course of the last year, the Breast Cancer Working Group (BCWG) has had a series of discussions and meetings to examine the problem of improving breast cancer patient outcomes. Recognising that medicines alone are not the solution but also that prevention, treatment standardisation, communication and education of both patients and providers and changing behaviours to refocus on patient outcomes would be part of the broader solution, participants nonetheless chose to focus on medicines to begin with. Participants acknowledged that this is where common ground and progress could be built initially across stakeholders in the Group. The Group has agreed a set of indicators and measures for assessing value in new breast cancer medicines as well as highlighted a pressing need for early stage interactions across industry, payer and regulators with patient- and citizen-advocate representation and provider inputs.

The consensus throughout the process has been that no single stakeholder, working alone, can create the changes needed in isolation; any successful effort to improve the healthcare delivery system in place to serve breast cancer patients will need to be the product of a collaborative approach across all. A Working Group participant welcomed this process as an opportunity to *"advance precision medicine, by discussing from the beginning what should be done, from preclinical target identification through drug candidate generation,"* while bringing all stakeholders together for a *"shared journey, working with the payer and the patient, to drive to optimal outcomes for all."*

Working Group recommendations

Developing a Shared Value Framework approach

The BCWG collaboratively developed a Shared Value Framework as a systematic approach to provide increased consistency of views across stakeholders on how new medicines can be assessed, demonstrated, captured and rewarded. The Group has identified a tiered model of value indicators to assess new medicines in breast cancer (details on consensus value indicators and measures in breast cancer are provided in Appendix C). Although the model is disease specific, many elements of it may be broadly applicable. The model consists of a base of therapeutic value indicators applicable to a specific disease followed by generalisable measures of economic impact and nation-specific economic and societal indicators). The model is illustrated below.



Earlier multi-stakeholder consultation

The Working Group concluded that a consensus view of indicators and measures for describing the value of a medicine, while necessary, is not enough on its own to resolve the ambiguities inherent to drug development. For industry to focus on developing medicines that society truly values, all stakeholders need to facilitate the exchange and spread of pertinent information concerning experimental breast cancer treatments early in the development process. As a consequence, the Working Group strongly supports early multi-stakeholder consultations to better align evidence requirements and clinical trial design to support both licensing and reimbursement. Such consultations, for example, would allow all parties to better align on the methodology or principles to define the appropriate standard of care to use as a comparator and clarify diagnostic requirements and QoL issues earlier in the development process of a medicine.

Consequently, piloting early multi-stakeholder consultations in drug development is potentially a rich source of value, giving greater:

- Alignment in resource allocation for industry, payers and regulators
- Pipeline horizon scanning opportunities to payers, physicians and patients, providing better data earlier to make more informed decisions
- Stakeholder alignment on the specific pre- and post-launch activities needed to assess and demonstrate the value of a new medicine, increasing alignment in clinical practice and guidelines for patients and providers with regulatory and reimbursement guidance.

Early consultation processes are not new across the EU. The gap is usually in the lack of the systematic involvement of payers. Based on learning of existing consultation processes, observing the following points is likely to lead to success:

- Encourage specificity of questions and content, and ample preparation time.
- Create an open environment receptive to unconstrained dialogue and learning (e.g. non-binding outcomes consistently arises as a principle that supports this environment).

- Foster close interaction within and amongst stakeholders.
- Publish findings from pilots to inform other innovators.

The path forward: pilots to test the Working Group's recommendations

The BCWG recommendations have been reported to the European Healthcare Innovation Network on 22 January 2010 meeting in London. The Network is committed to moving forward from theoretical discussions to piloting the Group's recommendations, and is currently seeking institutions within EU Member States to design and participate in pilot consultation processes using assets committed by industry sponsors. Institutional support for public sector participation in these pilots is seen as key. Pilots will be across, not simply within, member states to avoid fragmentation of guidance and value indicators, although there will need to be some recognition of Member State specific issues. Pilots will involve the range of stakeholders who are key decision makers in valuing new medicines for registration and reimbursement.

In considering the design of pilots, participants sought to develop a process that is transparent and inclusive. Summarised below is their resulting initial design guidance:

- **Ensure institutional support for public-sector participation.** Participants recommended obtaining official sanction from organisations to enable decision makers to participate in the pilots, and encouraged those organisations to promote participation in a manner that allows flexibility and openness to pursue innovative processes and thinking. This could be achieved by setting clear expectations and governance principles and appropriately preparing pilot participants similar to the Working Group briefing processes. A related point is, in a payer's words, *"to seek out people who are able to think outside of their organisation and who are interested in thinking beyond their own role."*
- **Prototype pilots across, not simply within, Member States.** Participants recommended prototyping an early consultation process with actual medicines across a manageable subset of Member States. While acknowledging that this approach is *"quite ambitious,"* participants considered it a step toward alignment on the inputs used by the various Member States to evaluate new drugs according to their own different methodologies.
- **Balance the benefits of collaboration with the retention of role independence.** The tension between independence and collaboration between stakeholders is of particular importance, since a lack of collaboration would function as a *"gating factor for the success of new forms of interaction."* Participants acknowledged the need to *"nudge the balance toward greater collaboration"* while ensuring that public sector participants continue to act within the responsibilities set by their official roles.
- **Ensure process transparency while protecting confidentiality of content.** Participants agreed that the objectives, structure, participants and process details of the pilots should be fully transparent, yet acknowledged the need to protect outcomes

related to a specific compound to protect the confidentiality of medicines in an early stage of development.

- **Agree to non-binding outcomes.** Due to the innovative nature of the pilots, participants recommended that advice provided in the consultations should be non-binding and should not displace existing channels for regulatory and reimbursement approval.
- **Share lessons and general clinical guidelines derived from the pilots.** Working Group participants agreed that *"pilots need to be approached in the spirit of learning,"* with an opportunity and obligation to provide generalisable guidelines on non-competitive clinical questions after the pilots.

The pilots are an innovative prototype effort to develop a consistent methodology and process across stakeholders for assessing value in medicines based on the Shared Value Framework (SVF) approach. The effort is done in the spirit of experimentation, with the emphasis on non-binding outcomes, process transparency and openness of sharing any lessons learned to lower risks of participation to all. This calls for pragmatic, open-minded individuals and organisations that are willing to look beyond their traditional boundaries for solutions. Participants who have taken this journey reflect a sense of optimism that collaboration and shared perspectives can achieve the goals to be demonstrated by the pilots: *"It is a common theme among us* [participants] *that we are optimistic ... It is astonishing that there is a shared sense of values and we can each appreciate different perspectives. I am looking forward to seeing the real pilots. That is really exciting and I would love to see what comes out of that!"* declared a payer–adviser. As a regulator agreed, *"I would be so optimistic that it is possible to tear walls down. It may not be next year, but I think if such processes as we have seen here* [in the working group] *will continue.. I think it is possible to tear walls down in the future!"*

There is a growing acceptance across stakeholder groups that by overcoming barriers to collaboration and aligning on value across stakeholders, real progress can be made to address the rising cost of medicines and the declining rate of innovation. The initiative to create SVF for drug development, assessment and reimbursement thus far has engaged over 100 European healthcare leaders across eight Member States. Those involved share the view that the current model for bringing new medicines to market is unsustainable and that change will be required from all stakeholders. There is strong support for redefining how value in medicines can be more effectively demonstrated, assessed, captured and rewarded. As part of this work, stakeholders believe there is an important opportunity to better align evidence requirements and clinical trial design to support both licensing and reimbursement with the ultimate goal of supporting innovation and improving patient outcomes. The Network and its Working Groups are an important step on that journey. As one leading payer exclaimed, *"If you would have asked me 3 years ago if we could have arranged trilateral meetings between regulators, payers and industry, I would have said 'no way'. But now the time is ripe and all are eager to meet."*

About this document

The views expressed in this document represent those of the Breast Cancer Working Group, convened by the European Healthcare Innovation Leadership Network, a group of leading stakeholders from the public and private sectors committed to improving healthcare and economic wellbeing in the European Union and its Member States. This document is not intended to represent the particular policies or positions of the Working Group's individual participants or their affiliated organisations. This material is prepared by and the copyright of Tapestry Networks. It may be reproduced and redistributed, but only in its entirety, including all copyright and trademark legends.

Apendix A: European Healthcare Innovation Leadership Network members

Members

Member States

Czech Republic

- **Pavel Hroboň** | Former Deputy Minister |Ministry of Health

France

- **Eric Abadie** | Direction Générale | Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)
- **Noël Renaudin** | President | Economic Committee for Health Products (CEPS)

Germany

- **Rainer Hess** | Impartial Chairman | Federal Joint Committee (G-BA)
- **Wolfgang Schmeinck** | Beauftragter des Vorstandes | BKK Landesverband Nordrhein-Westfalen

Netherlands

- **Mike Leers** | Advisor - Board of Commissioners| CZ Healthcare Insurance Group
- **Martin van Rijn** | CEO | PGGM

United Kingdom

- **Mike Farrar CBE** | Chief Executive | National Health Service – North West
- **Sir Michael Rawlins** | Chairman | National Institute for Health & Clinical Excellence (NICE)
- **Professor Sir Mike Richards CBE** | National Clinical Director for Cancer & End of Life Care| St Thomas' Hospital

Pharmaceutical Innovators

- **Eddie Gray** | President, Pharmaceuticals Europe | GlaxoSmithKline
- **David Norton** | Company Group Chairman - Global Pharmaceuticals | Johnson & Johnson
- **Ulf Säther** | Regional Vice President, Europe | AstraZeneca

Other Key Constituents

- **David Byrne** | Former EU Commissioner, Health and Consumer Protection
- **Thomas Lönngren** | Executive Director | European Medicines Agency (EMA)
- **Anders Olauson** | President | European Patients' Forum
- **Sophia Tickell** | Executive Director | SustainAbility & Director | Pharma Futures

Apendix B: Breast Cancer Working Group participants

Medical subject matter experts

- **Jonas Bergh**, Karolinska Institute, Sweden
- **PierFranco Conte**, Universitaria di Modena, Italy
- **Jindřich Fínek**, University Hospital Plzen, Czech Republic
- **Luca Gianni**, University of Milan, Italy
- **Anthony Howell**, The Christie NHS Foundation Trust, UK
- **Christian Jackisch**, Klinikum Offenbach GmbH, Germany
- **David Khayat**, Pitié-Salpêtrière Hospital, France
- **Jan Lubiński**, Pomeranian Medical University, Poland
- **Miguel Martin**, Hospital Universitario San Carlos, Spain
- **Larry Norton**, Memorial Sloan-Kettering Cancer Center, USA
- **John Robertson**, University of Nottingham, UK
- **Karol Sikora**, CancerPartners UK, UK
- **Michael Untch**, HELIOS Klinikum, Germany

Payers, regulators, health economists, and advisors

- **Johannes Bruns**, Deutsche Krebsgesellschaft, Germany
- **Karl Claxton**, University of York, UK
- **Pierre Démolis**, Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)
- **Harald Enzmann**, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Germany
- **Pavel Hroboň,** formerly Ministry of Health, Czech Republic
- **Bengt Jönsson**, Stockholm School of Economics, Sweden
- **Bertil Jonsson**, Medical Products Agency, Sweden
- **Sören Olofsson**, Region Skåne, Sweden

Patient representatives

- **Els Borst-Eilers**, Dutch Federation of Cancer Patients, The Netherlands
- **Susan Knox**, EUROPA DONNA, European Breast Cancer Coalition *(OBSERVER)*

Industry representatives

- **Jim Baker**, Johnson & Johnson
- **Alan Barge**, AstraZeneca
- **Paolo Paoletti**, GlaxoSmithKline

Appendix C: Breast Cancer Consensus Value Indicators and Measures

Therapeutic value components		
Value component	**Measure**	**Timing of demonstration**
▪ **Current endpoints for assessing value for registration/reimbursement purposes (relevant usage determined by context of the disease stage)**		
Survival	▪ Median overall survival (mOS) segmented by disease stage	▪ Pre-launch for metastatic; post-launch potentially in adjuvant setting
Tumour stabilisation	▪ Progression-free survival (PFS) or disease-free survival (DFS), dependent on disease stage context	▪ Pre-launch, with potential link to OS, dependent on disease context
Reduction of tumour size	▪ Objective response rate (ORR) ▪ Duration of response	▪ Pre-launch, with link to mOS
Prevention of reoccurrence	▪ Rate of local reoccurrence of tumour	
Inhibition of metastasis	▪ Rate of metastasis (as proxy for impact on survival)	
▪ **Emerging or scientific endpoints useful for decisions on drug development**		
Delayed disease progression	▪ *Circulating tumour cells* ▪ *DNA in plasma*	▪ *Pre-launch, need link to OS (these indicators are considered very early in development, and have yet to accumulate the body of evidence required to be convincing as clinical endpoints)*
▪ **Drug safety, side effects, quality of life (QoL)**		
Increased tolerability	▪ Percentage discontinuing treatment relative to the comparator	▪ Pre-launch; post-launch re-examination if possible
Reduced toxicity	▪ Total Grade 3 and 4 side effects (rate of serious adverse events) ▪ Percentage occurrence of adverse events impacting treatment decisions	▪ Pre-launch; post-launch re-examination if possible

Note: *An italicised breast cancer value indicator signifies an indicator where consensus on usage for registration and reimbursement purposes remains open.*

Therapeutic value components (*continued*)		
Value component	**Measure**	**Timing of demonstration**
▪ **Drug safety, side effects, quality of life (QoL)** *(continued)*		
Patient-reported QoL	▪ *Percentage reporting meaningful clinical difference in QoL (measure and collection design to be agreed on – current lack of consensus)*	▪ *Pre-launch; post-launch re-examination if possible*
QoL	▪ *Q-TWiST: Quality-Adjusted Time Without Symptoms of Disease or Toxicity of Treatment*	▪ *Pre-launch; post-launch re-examination if possible*
▪ **Innovation**		
Level of innovation	▪ Linked to efficacy or impact on safety/side effects/QoL ▪ Advancement of field of treatment	▪ Pre-launch

Economic value components		
Value component	**Measure**	**Timing of demonstration**
Illustrative cross-model economic inputs	▪ Treatment price (or price ranges dependent on treatment scenarios) ▪ Utilisation rate ▪ Total acquisition cost ▪ Patient life-years gained ▪ QoL or societal impact on life-years gained	▪ Pre-launch; post-launch re-examination if possible (e.g. for cost)

Systemic economic indicators, dependent on health system		
Value component	**Measure**	**Timing of demonstration**
Healthcare system cost	▪ Total net cost to healthcare system per year	▪ Pre-launch model; post-launch re-examination
Pharmaceutical cost	▪ Total net cost to healthcare system pharmaceutical spending per year	▪ Pre-launch model; post-launch re-examination
Patient-borne cost	▪ Total net cost borne by patients per year	▪ Pre-launch model; post-launch re-examination