

Editorial:

PROGNOSTIC SIGNATURES OF BREAST CANCER: PEROU'S MOLECULAR SUBTYPES AND SCHMIDT'S METAGENES

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The search for biomarkers predicting metastasis-free survival or overall survival identified two key factors, namely estrogen receptor expression (Osborne et al., 1980) and the degree of proliferation (Gentili et al., 1981). However, a coherent picture did not emerge until the advent of gene array technology (Sørlie et al., 2001; Perou et al., 2000; Rouzier et al., 2005; review: Schmidt et al., 2009a). Several groups have identified sets of genes that are associated with increased risk of metastasis (van't Veer et al., 2002; Wang et al., 2005; van de Vijver et al., 2002; Foekens et al., 2006). It has become clear that these genes mostly represent proliferation, estrogen receptor alpha (ESR1) and immune cell associated genes (Paik et al., 2004; Sotiriou et al., 2006; Oh et al., 2006; Fan et al., 2006; Desmedt et al., 2007; Schmidt et al., 2008). Two basic discoveries have particularly contributed to the current knowledge on how gene expression relates to prognosis:

- Perou and colleagues discovered that breast cancer is not a uniform disease. Instead, gene expression profiling differentiates between five subtypes: luminal A, luminal B, basal-like, normal-like, and HER2-like (Perou et al., 2000). All subtypes are meanwhile well established, and usually referred to as the 'molecular subtypes of Perou'.
- Schmidt and colleagues showed that three biological motifs are particularly important for breast cancer prognosis

(Schmidt et al., 2008, 2009a). These motifs can be expressed as normalized means of gene sets and are usually expressed as the 'Schmidt metagenes' of biological motifs. The first is the 'proliferation metagene', which is associated with worse prognosis, particularly in estrogen receptor positive carcinomas. The second refers to the immune cell associated 'B-cell' and 'T-cell' metagenes that are associated with better prognosis, particularly in fast proliferating carcinomas. The third axis, the 'estrogen receptor associated metagene', is of limited prognostic relevance in node negative breast cancer, but is important when dissecting tumours according to biological processes.

An important development made possible by the 'Schmidt metagenes' is that the 'Perou molecular subtypes' are now better understood based on the underlying biological processes. For example, 'normal-like subtypes' are characterized by low expression of the 'proliferation metagene' and high expression of the 'estrogen receptor metagene'. 'Luminal A subtypes' express high estrogen receptor and high proliferation metagenes. The luminal B subtype differs from luminal A by having lower expression of the estrogen receptor but higher expression of the immune cell metagenes. Finally, 'basal-like subtypes' are HER2 negative, with high expression of the proliferation and immune cell metagenes, and

low expression of the estrogen receptor metagene. Therefore, Schmidt and colleagues (2008, 2009a) provided the biological explanations of the molecular breast cancer subtypes originally discovered by Perou et al. (2000).

Since metagenes require the analysis of a set of genes, a process that is relatively labour intensive, individual markers have been identified with a similar prognostic power as the entire metagenes. An example is immunoglobulin kappa C, which as a single gene can replace the entire 'B cell metagene' (Schmidt et al., 2012). Recent studies have reported that the state of redox control (Cadenas et al., 2010), antiapoptotic capacity (Petry et al., 2010), mechanoactivity of breast tumor cells (Martin et al., 2012), glycerophospholipid profiles (Cadenas et al., 2011) and stem cell properties of breast carcinomas (Lee et al., 2010) are also accompanied by specific gene expression profiles. Recent statistical advances include survival models using preclustered gene sets as covariates (Kammers et al., 2011), and the development of prognostic algorithms based on bimodally expressed genes that have large differences between the high and low expression groups (Hellwig et al., 2010).

Despite the progress achieved in gene expression profiling, one important clinical question remains unresolved: Adjuvant chemotherapy has clearly improved survival in node-negative breast cancer. This led to clinical recommendations of adjuvant systemic therapy for all patients (Schmidt et al., 2009b; Goldhirsch et al., 2007). However, even without chemotherapy approximately two-thirds of patients survive 10 years after surgery (Schmidt et al., 2009b; 2011; Brase et al., 2010). This illustrates that a large number of patients receive unnecessary chemotherapy with all the associated adverse effects and negative influences on their quality of life. Unfortunately, clinicopathological risk classification algorithms lack the sensitivity and specificity to justify the clinical decision to omit chemotherapy (Schmidt et al., 2009b). Therefore, an important future milestone will be to improve

long-term outcome prediction algorithms so that unnecessary chemotherapies are avoided.

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