The Breast Centre
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The Breast Centre
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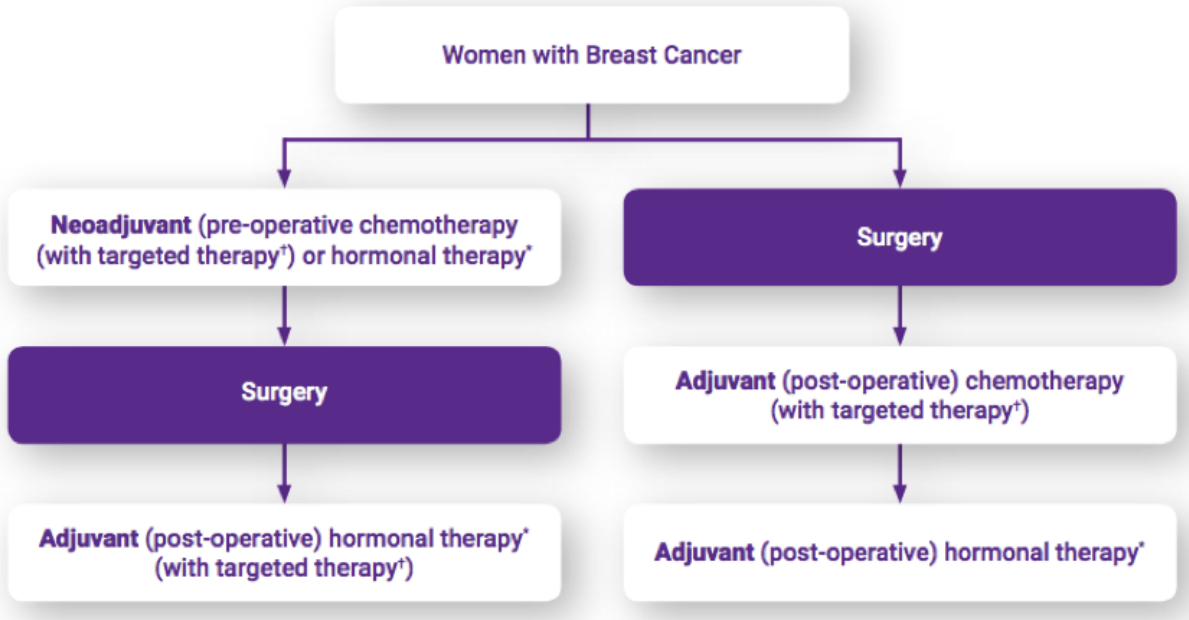
ST VINCENT'S PRIVATE HOSPITAL EAST MELBOURNE

Making Initial Breast Cancer Treatment Decisions

Patients who receive a new breast cancer diagnosis are understandably anxious to find out as soon as possible what their treatment will entail. While it is rarely possible at the time of the initial diagnosis to accurately predict exactly what treatment will be required in their particular situation, often with the information obtained from the clinical breast examination, initial breast imaging and the needle core biopsy pathology, it is possible for some preliminary predictions to be made.

As the breast surgeon is usually the first specialist with whom the patient meets, part of my role is to explain the overall treatment process, not just the surgical component, and to explain the rationale for considering other forms of treatment, such as drug therapy and radiotherapy, in addition to surgery. Increasingly this discussion also involves the potential "sequencing" of treatment modalities, as it is no longer automatic that surgery is the initial treatment of choice in all women with operable breast cancer.



† Targeted therapy eg. trastuzumab is for HER2 positive breast cancer
* Hormonal therapy is for hormone receptor positive breast cancer

Treatment Sequencing Options

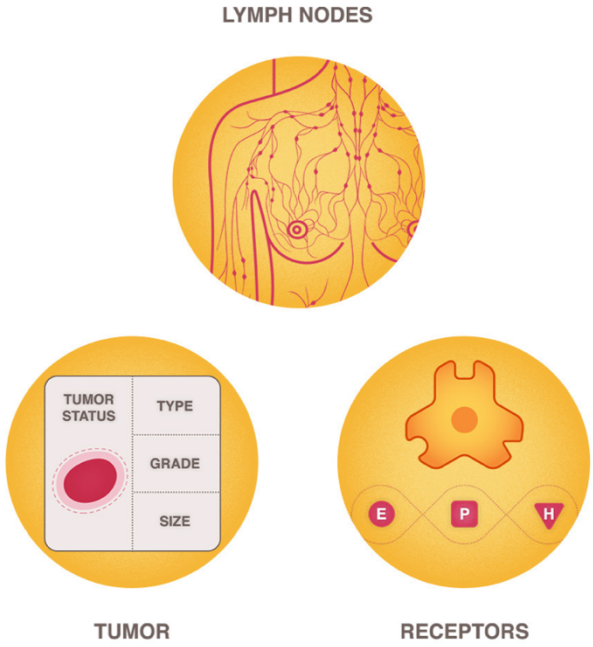
The modern management of early breast cancer is based on both "**tumour burden**", as assessed by the size of the tumour and nodal status and increasingly, "**molecular subtype**".

THE FIRST STEP:

When I see a patient with a new, operable, invasive breast cancer diagnosis, there are several important pieces of information in which I am interested, because they are crucial in informing the nature and sequencing of the initial breast cancer treatment.

These factors are:

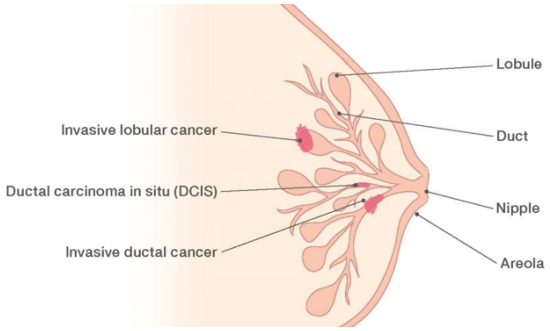
1. Molecular subtype of the cancer on needle core biopsy
2. Tumour Burden: Tumour size and Axillary Nodal Status



1. Molecular Subtype

In days gone by, the only information usually provided by the diagnostic needle biopsy was the confirmation of the breast cancer diagnosis. Pathology has advanced significantly in recent years, and the level of information about the biological nature of the breast cancer that we currently obtain from the core biopsy pathology report was previously only available (if it all) on the surgical excision specimen. This information not only potentially influences the sequencing of treatment, but also enables the breast surgeon to counsel the patient at the time of diagnosis about the likelihood that chemotherapy, targeted agents and/or hormonal blockade will form part of their treatment, either prior to or after surgical removal of the cancer. The pathological information that may be obtained from the diagnostic breast core biopsy includes:

- **Histological Type:** The two most frequent histological types of breast cancer are invasive ductal cancer-often described as being of "no special type" (NST)- (70-75%) and invasive lobular cancer (ILC)-(10-15%). The other 18 subtypes are uncommon (0.5-5%).



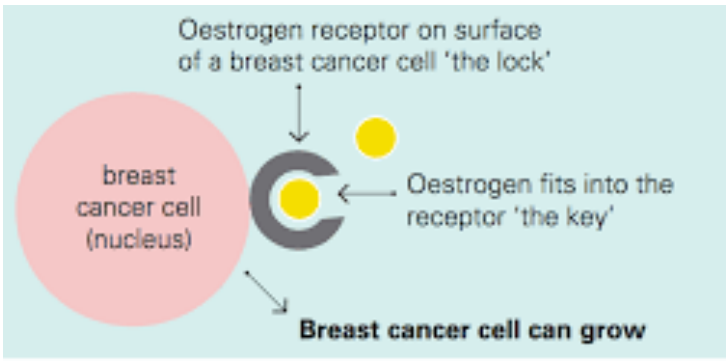
Histological Subtypes.

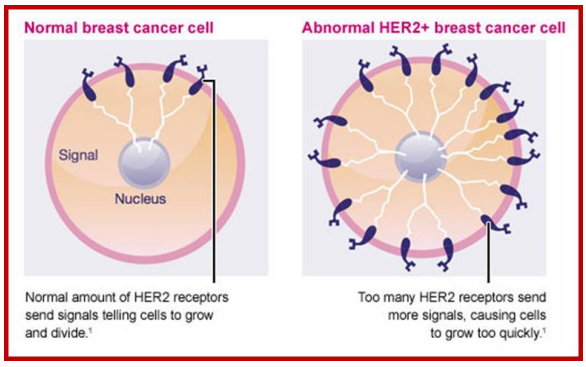
Grade 1	Low grade	usually slow growing cancer cells and structures look more like normal breast cells
Grade 2	Intermediate grade	intermediate growth rate the cancer has fewer features of normal breast tissue
Grade 3	High grade	fast growing cancer cells look very different from normal breast cells

Grades of Breast Cancer

- **Grade:** The grade of a breast cancer indicates the pattern of the cancer cell growth and how fast the cancer cells are growing. The grade is numbered from 1 to 3: grade 1 being the least aggressive. A provisional or estimated tumour grade is often reported on the core biopsy, but the final grade of the tumour can only be determined on the operative specimen.

- **Receptor Status:** Oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2). Tumours expressing ER and/or PR are termed 'hormone receptor-positive' (HR+) breast cancers. Those expressing human epidermal growth factor receptor 2 are described as HER2 positive (HER2+) and can be hormone receptor positive or negative. On occasions, the core biopsy HER2 result immunohistochemistry is equivocal, and the final HER2 status of the tumour may not established until a definitive (ISH) test is performed. This is usually undertaken on the operative specimen, but if preoperative/neoadjuvant drug therapy is being considered, it can be performed on the core biopsy specimen. Tumours not expressing ER, PR or HER2, are called 'triple-negative' breast cancers (TNBC).





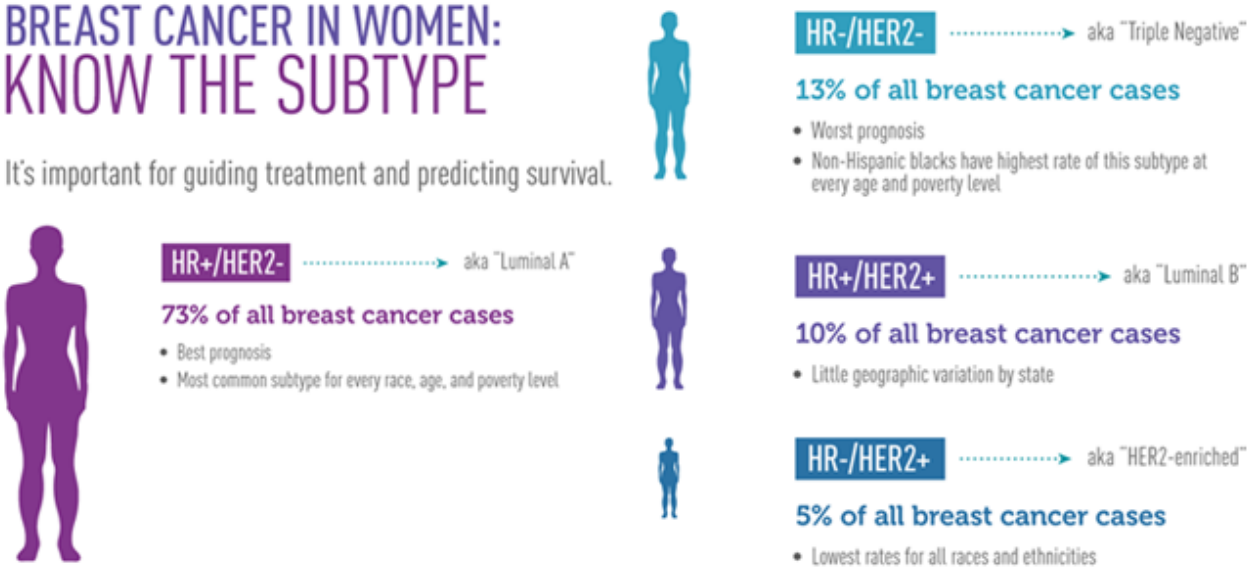
- **+/- Ki 67**: Ki-67 is a protein in cells that increases when cells are dividing, and is a marker of proliferation. It is reported as the percentage of cancer cells that contain Ki-67. The more positive cells there are, the more quickly the cancer is dividing and growing.

Breast cancer core biopsies which report receptor status allow tumours to be divided into four main receptor subtypes, as tabled below, which I find helpful in enabling me to immediately develop in my own mind and also discuss with the patient, a preliminary treatment "template".

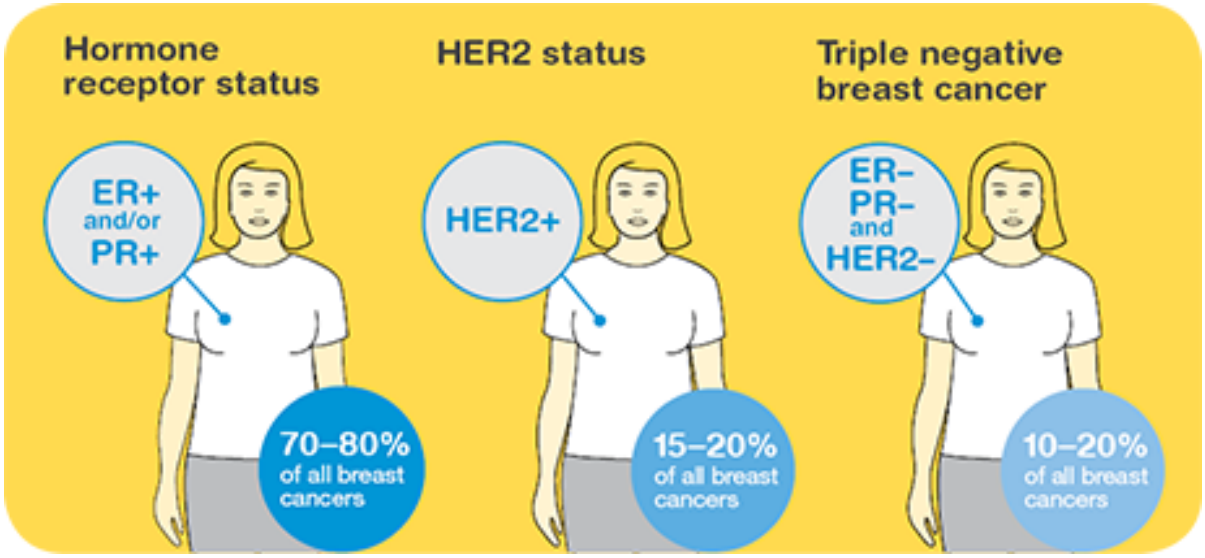
4 Major Breast Cancer Receptor Subtypes

Subtype 1 Hormone Receptor HR +ve HER2 -ve (65%)	**Subtype 3** Hormone Receptor HR +ve HER2 +ve (10%)
Subtype 2 Hormone Receptor -ve HER2 -ve (15%) Triple Negative'	**Subtype 4** Hormone Receptor -ve HER2 +ve (10%)

- HR+/HER2- tumours form the most common receptor subtype, and endocrine therapy to block ER activity is recommended all patients with ER+ and/or PR + breast cancers. Cancers which are subtype 1 do not automatically prompt a recommendation for chemotherapy, and as often there may not even be a need for chemotherapy in these cancers, preoperative chemo is therefore not commonly considered, and the majority of subtype 1 tumours (HR+/HER2-) are treated with initial surgery. Decisions regarding postoperative (adjuvant) systemic (drug) therapy are then made after surgery, based on the operative pathology results, sometimes with the additional assistance of a genomic test such as Oncotype DX.
- Cancers which are either HER2+ or triple negative, fall into receptor subtypes 2, 3 and 4 in the table above, and there will almost always be a recommendation for chemotherapy +/- HER2 targeted therapy at some point in the treatment trajectory. What sort of chemotherapy, for how long and whether it is administered before or after surgery is influenced by the **"tumour burden",** which is determined by the **"size"** and **"nodal status"** of the cancer, not the biological **"molecular subtype".**

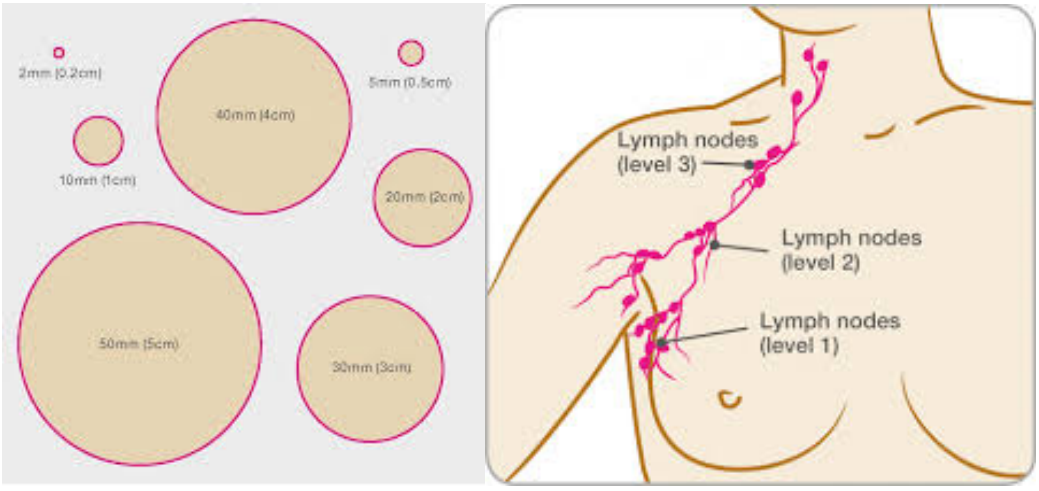


The tumour biological subtype therefore determines what class of drug therapy is appropriate, and the size and nodal status allow that decision making to be further refined. In general terms, as chemotherapy attacks rapidly dividing cells, it tends to be most effective in faster growing cancers, which are typically high grade and HR-, as these cancers are usually the most "chemosensitive". As the receptor status of the tumour is so important in determining treatment, in patients in whom a breast cancer diagnosis has been confirmed on core biopsy, it is helpful if the receptor status results are available prior to the initial appointment with the breast surgeon, as the consultation is then more informative.



2. Tumour Burden: Tumour Size and Axillary Nodal Status

With access to accurate state of the art modern breast imaging, including 3d mammography with tomosynthesis, breast MRI and the routine targeted preoperative sonographic assessment of the axilla, together with image guided needle biopsy of any abnormal axillary nodes, we now have more information available to us preoperatively than in the past regarding the estimated "tumour burden".



- Tumour size

As assessed by:

- Clinical examination (if there is a palpable "lump" present)
- Mammography- bilateral, preferably 3D digital mammography with tomosynthesis
- Ultrasound- formal ultrasound performed by the radiologist, sometimes supplemented by bedside ultrasound performed by the breast surgeon to correlate clinical and imaging findings.

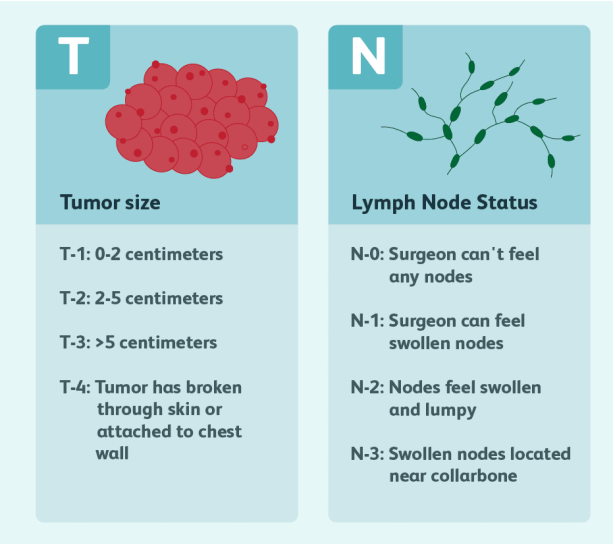
- +/- MRI

The estimated size of the tumour, as assessed by some or all of the modalities above, is important in helping to determine the most appropriate form of surgery to the breast.

- **Axillary Nodal Status**

As assessed by:

- Clinical examination- low sensitivity, other than the heavily involved axilla
- Targeted ultrasound-ultrasound guided needle biopsy, either fine needle aspirate (FNA) or preferably core biopsy, of any axillary nodes on the side of the breast cancer that are even marginally abnormal on ultrasound.



Armed with information on the tumour molecular subtype and tumour burden, it is possible to commence treatment decision making.

The two pillars of breast cancer treatment are "**locoregional"** and "**systemic"** treatment. "Locoregional" therapy refers to the local treatment of the breast and axilla, with surgery +/- local radiotherapy and "systemic "therapy refers to <u>all</u> types of drug therapy, including chemotherapy, biologic targeted therapy, and endocrine therapy.

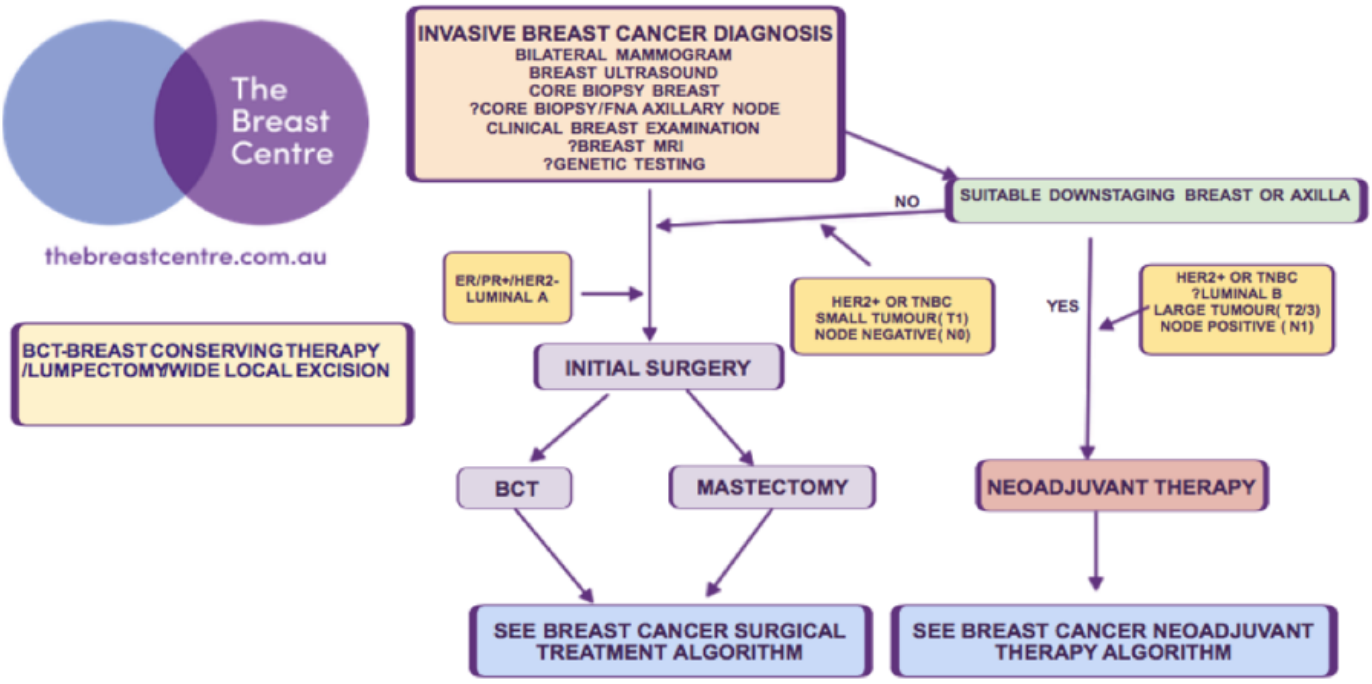
"Adjuvant" (post-operative) systemic therapy is administered in addition to local therapy to treat any potential "micrometastatic" disease, and thus hopefully prevent distant recurrence, and is tailored to the cancer subtype and risk of recurrence. "Neoadjuvant" (preoperative) systemic therapy targets local disease (breast/axilla) as well as potential micrometastatic disease elsewhere in the body.

Armed with information on the tumour molecular subtype and tumour burden, it is possible to commence treatment decision making, in particular the potential treatment sequencing, as while surgery remains the first treatment recommended for the majority of patients with early breast cancer, preoperative or neoadjuvant chemotherapy is being used with increasing frequency in the multidisciplinary treatment of patients with operable breast cancer.

In the past, the recommendation for chemotherapy was based largely on tumour burden, and as such patients still tend to associate chemotherapy with poorer prognosis, larger and heavily node positive cancers. As tumour molecular subtype now so heavily influences the recommendation for chemotherapy, when it appears inevitable that chemotherapy will be recommended based on the tumour biology/molecular subtype of the diagnostic core biopsy, I think it is appropriate to advise patients of this early on. This serves to reinforce to the

patient, the concept that the recommendation for chemotherapy is based on the likelihood that the tumour will be “chemosensitive”, and that the requirement for chemotherapy does not necessarily reflect a more advanced cancer or a worse prognosis, but reflects the fact that chemotherapy is the most appropriate and effective drug therapy for that molecular subtype of breast cancer.

The management of breast cancer is a step by step process, with the outcome of each stage often determining what is required next, and as such, I find a helpful way of outlining the possible treatment pathways is with the use of treatment algorithms, which outline the decision making process in a flow chart format. Practices change over time, with the introduction of modern surgical techniques and new drug therapies, and I have developed a number of my own breast cancer treatment algorithms based on the way I currently work through the decision making in each individual patient, all of which can be found on the website.



Jane O’Brien Breast Cancer Treatment Sequencing Algorithm