PRÄGO: Pilot project to evaluate the standardized use of gene expression assay OncotypeDX in non-metastatic HR-positive HER2-negative breast cancer

Study Protocol
Version 1.0

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Table of Content

1. Basic Data

1.1 Study title

PRÄGO: Pilot project to evaluate the standardized use of gene expression assay OncotypeDX in non-metastatic HR-positive HER2-negative breast cancer

1.2 Study Coordination

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1.3 Coordinating Institution

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University Hospital Schleswig-Holstein Campus Lübeck
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1.4 Participating Study Sites

Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein Campus Lübeck, Germany

Department of Gynecology and Obstetrics, University Hospital Hannover, Germany

Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein Campus Kiel, Germany

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Klinikum Bremen-Mitte, Bremen, Germany

Paracelsus-Klinik Henstedt-Ulzburg, Germany

Asklepios Klinik Barmbek, Hamburg, Germany

imland Klinik Rendsburg, Rendsburg, Germany

Kiel-Mitte

SLK Kliniken Heilbronn

DIAKO Rotenburg

1.5 Potential conflicts of interest

Prof. Dr. Achim Rody received honoraria for lectures and advisory role from Exact Sciences. PD Dr. Maggie Banys-Paluchowski and Dr. Kerstin Muras declare that no potential conflicts of interest exist regarding the current project.

2. Introduction

Approximately 69,000 women develop breast cancer yearly in Germany, making this oncological entity the most common female malignancy accounting for 32% of all new cancer cases in Germany [1].

Based on the immunohistochemical assessment of surrogate markers estrogen receptor (ER), progesterone receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2) and proliferation marker Ki-67, tumors can be categorized into one of several subtypes. The St. Gallen classification included four intrinsic subtypes referred to as: Luminal A, Luminal B (HER2-negative and HER2-positive), HER2-positive (non-luminal) und basal/triple-negative [2]. Currently, immunohistochemistry is considered

gold standard for assessment of the above-mentioned markers, however an interobserver variability has been reported [3, 4].

The accurate estimation of the prognosis in early hormone receptor (HR) positive HER2-negative breast cancer remains challenging. Multigene expression assays were developed to address this important issue through improved risk stratification and evalution of individual chemotherapy benefit [5-10]. Using established molecular mehods such as RT-PCR and micro-RNA gene expression measurement, these assays offer the possibility of recurrence risk estimation on an individual level. One of these tests is the OncotypeDX test (Exact Sciences), approved by the German Federal Joint Committee (Gemeinsamer Bundesausschuss = GBA) [5]. OncotypeDX is based on a qRT-PCR analyzing 21 genes involved in tumor proliferation, apoptosis, and signal transduction. The result of the assay is a so-called Recurrence Score, a risk score that can be considered when choosing to recommend or forego chemotherapy [5, 11, 12]. According to the current guielines of the AGO Breast Committee, gene expression assays should be performed in selected patients [AGO: +; Level of evidence: Ib] [7, 13]. For patients with HR+ HER2- breast cancer treated within the ASV reimbursement system (ASV = Ambulante Spezialfachärztliche Versorgung; https://www.g-ba.de/themen/asv/), the OncotypeDX test can be prescribed if a patient fulfils pre-defined criteria [14]:

- ER-positive HER2-negative and
- Age > 35 Jahre and
- N0 and
- Tumor size > 1 cm
  with one of the following criteria:
  - G2 or
  - Ki-67 > 10% ≤ 30%
  but not G3 or Ki-67 > 30%

or

- ER-positive HER2-negative and
- Age > 35 Jahre and
- N+ (1-3 positive lymph nodes)
  with one of the following criteria:
  - G1 or G2 or Ki-67 > 10% ≤ 30%
  but not G3 or Ki-67 > 30% [14]

3. Study design

Prospective multicenter non-interventional investigator-initiated study

3.1 Study aims

- Evaluation of the standardized use of OncotypeDX assay in the clinical routine
- Evaluation of the standardization processes involved in the decision to order a gene expression assay:
    - in-house standardization
    - comparison between hospitals
    - comparison between regions
- Evaluation of reasons for omitting an OncotypeDX test despite ASV fulfilled reimbursement criteria
- Evaluation of the correlation between gene expression assay result (core biopsy) and response to neoadjuvant chemotherapy in patients treated in the neoadjuvant setting
- Evaluation of the treatment decision impact of gene expression assay assessed in the core biopsy material
- Evaluation of the treatment decision impact of gene expression assay assessed in the surgical specimen

3.2 Inclusion and exclusion criteria

Inclusion criteria

- Primary non-metastatic breast cancer
- Hormone-receptor positive HER2-negative status
- Age ≥ 18 years
- OncotypeDX test performed in the clinical routine within the ASV reimbursement criteria
- Signed informed consent

Exclusion criteria

- Age < 18 years
- Patients with impaired consent capacity
- Patients not receiving an OncotypeDX test
- Patients receiving an OncotypeDX test outside of ASV reimbursement plan

3.3 Study collective

600 patients

20-30 breast cancer centers participating in the ASV reimbursement system

3.4 Study duration

12 months

4. Safety issues

PRÄGO is a non-interventional study including data from the clinical routine. All patients receiving OncotypeDX withing the ASV reimbursement system during study period who provided informed consent will be included in the study. Patients will be treated at study sites according to current guidelines. Study participation does not influence treatment decisions. No study-specific interventions are planned. Patients with impaired or questionable consent capacity will not be included in the study.

5. Data management and analysis

Pseudonymized OncotypeDX test results will be documented in an Excel and SPSS file, together with relevant tumor-related data (such as TNM stage, age, receptor status etc.). The password-secured database will be stored at the IT server of the Department of Gynecology and Obstetrics of the UKSH Campus Lübeck. It will be accessible only to the study team. Data will be stored for 3 years and anonymized afterwards.

6. Risk-benefit analysis

Neither risks nor benefits are expected for individual study participants. Only data from the clinical routine are documented in the study. No study-related interventions are performed.

7. References

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