The Future of Personalized Treatment

Overview

- BOSCH in Healthcare
- Vivatmo: Breath Analysis for improved Asthma Therapy
- Vivalytic: Open Modular Platform for Automation of Molecular Diagnostics Assays
- Detection of Infectious Diseases
- Potentials in Oncology: Patient Stratification and Monitoring of Targeted Therapies
- Summary
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Citation from Robert Bosch

“...It is inherent to the nature of medicine that its greatest concern is to cure the suffering and, where this is not possible, to alleviate pain.”

______________________________ ROBERT BOSCH

1941
## The Future of Personalized Treatment

### History of the Robert-Bosch-Hospital

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1915</td>
<td>Entrepreneurial foundation initiative: Founding of the “Stuttgarter Homöopathie Krankenhaus GmbH” by the industrial entrepreneur Robert Bosch.</td>
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<tr>
<td>1936</td>
<td>The Foundation of the Robert-Bosch-Krankenhaus Robert Bosch’s 76th birthday and the 50th anniversary of his company, the Robert Bosch GmbH, presented the occasion for realizing the plans to build a hospital as a foundation.</td>
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<tr>
<td>2006</td>
<td>Acquisitions of Klinik Schillerhöhe and Klinik Charlottenhaus Klinik Schillerhöhe in Gerlingen is a specialized healthcare center for the treatment of lung diseases. The Klinik Charlottenhaus in Stuttgart’s east districts is specialized in gynecology, obstetrics and plastic surgery.</td>
</tr>
<tr>
<td>2008</td>
<td>Perspectives – Building for the future The comprehensive modernisation and extension of the hospital was completed after six years.</td>
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</tbody>
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Bosch Healthcare Solutions

**Our vision**

With innovative solutions “Invented for life”, we improve quality of life and help to optimize global healthcare.
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**NEED**
- Non-invasive breath analysis with a patient device for measurement at home.

**MARKET**
- With Vivatmo me approximately 13 m patients can be reached in 2023.¹
- More than 330 m people worldwide suffer from asthma.²
- The number of fatal casualties caused by asthma worldwide is around 383,000 annually.³

**PRODUCTS**
- Vivatmo pro for physicians
- Vivatmo me for patients
- Vivatmo app for patients

**CORE COMPETENCIES**
- Sensors
- Miniaturization
- Interconnectivity

**USE CASES**
- Diagnostic support
- Asthma therapy management
- Asthma self-monitoring

With the Vivatmo system, we support the best possible patient therapy and help to significantly improve asthma patients’ quality of life.

¹ Internal market assessment
² The Global Asthma Network 2014
³ WHO Mortality Database 2016

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The global market volume of molecular diagnostics is estimated to EUR 9.5 bn in 2021.\(^1\) Infectious diseases are the largest market segment in molecular diagnostics.\(^2\)

The wide range of applications and the quick and easy performance of the tests enable physicians to diagnose and treat patients faster.

\(^1\) Markets and Markets: Molecular Diagnostics Market by Application – Forecast to 2021
\(^2\) Markets and Markets: IVD Market by Product Technology by Application – Forecast to 2021
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Automation of complex Molecular Diagnostic Workflows

Conventional: complex **manual** workflow in diagnostics labs

- Sample Preparation
- Cell Lysis (Disruption)
- DNA Extraction
- DNA Amplification
- Bioanalytic Detection

Sample: e.g. blood, swab, sputum

Fully automated diagnostic workflow via modular Bosch Lab-on-Chip platform

Lab-on-Chip: Integrated microfluidic System for **Automation** of Diagnostics

Depending on the application, test results can be available within 30 minutes.

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Flexible Modular Platform

**Universal Processing Station:** Vivalytic Analyser

**Application-specific Disposable Cartridges**

**Key Benefits**

- Cartridge as closed system (avoids contamination)
- All reagents stored on cartridge, only sample loading needed
- Storage of cartridge @ room temperature
- High degree of Multiplex diagnostics (up to ~100 characteristics/sample)
- Independent multiple PCR- and detection-chains
- Standard detection methods (μArray, PCR, qPCR, melting curve)
- Random access device
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Vivalytic Analyser

Optics and camera
Mechanics
cartridge feeder, clamping, reagent release
Software
incl. clinical information system
Connected and combinable
The Bosch Analyser supports HL7, GDT, and POCT-1A out-of-the-box.
Connectivity options include Ethernet, WLAN, Bluetooth, and GSM.

Electronics
power supply, hardware control, image acquisition
Mechanics
cartridge feeder, clamping, reagent release
Software
incl. clinical information system
Connected and combinable
The Bosch Analyser supports HL7, GDT, and POCT-1A out-of-the-box.
Connectivity options include Ethernet, WLAN, Bluetooth, and GSM.

Pneumatics
pumps, valves, manifolds
Mechanics
cartridge feeder, clamping, reagent release
Software
incl. clinical information system
Connected and combinable
The Bosch Analyser supports HL7, GDT, and POCT-1A out-of-the-box.
Connectivity options include Ethernet, WLAN, Bluetooth, and GSM.

Thermal management
Heaters, ventilators
Man-machine-interface
touch-display, scanner
Software
incl. clinical information system
Connected and combinable
The Bosch Analyser supports HL7, GDT, and POCT-1A out-of-the-box.
Connectivity options include Ethernet, WLAN, Bluetooth, and GSM.

Ultrasonics
universal sample lysing
Software
incl. clinical information system
Connected and combinable
The Bosch Analyser supports HL7, GDT, and POCT-1A out-of-the-box.
Connectivity options include Ethernet, WLAN, Bluetooth, and GSM.

Fluidic layer
Elastic Membrane (carrier film)
Reagent bars
Cover
Lab-on-Chip cartridge
Exploded view of cartridge components

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Vivalytic Cartridge

Cover
Lab-on-Chip cartridge
Fluidic layer
Reagent bars
Elastic Membrane (carrier film)
Pneumatic layer
PC seal film (carrier film)
Exploded view of cartridge components

Reagent bars
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Operation of Vivalytic

1. Scan Sample Code
2. Scan Cartridge Code
3. Load Sample and close Lid
4. Enter Cartridge and push START

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Business model

“So, you are like Apple. The analyser is your iPhone, and others can develop their apps for it. That’s genius!”

- Open Platform Solution
- Bosch Technology for Automation of any Molecular Diagnostics Workflow
- Broad Test Portfolio
- Fast Market Access for new Tests
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Processing of Infectious Disease Assay

Sample Input
50…1000μl Blood, urine, tissue, swabs, sputum

Reagent storage at room temperature for 2 years

Sample purification
Bacteria, virus, fungi, human cells – Purification of DNA and RNA

Detection
2 individual strands for qPCR and melting curve
50x Multiplex μArray
Quantitative and semi-quantitative detection
Combination of detection mechanisms possible

Amplification
2 individual strands for PCR
Highly sensitive PCR

Detection
2 individual strands for qPCR and melting curve
50x Multiplex μArray
Quantitative and semi-quantitative detection
Combination of detection mechanisms possible

Reagent storage at room temperature for 2 years

Sample purification
Bacteria, virus, fungi, human cells – Purification of DNA and RNA

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Cartridge pneumatic actuation principle

- Automation of complex test protocols
- Small volumes
- Precisely controlled conditions

valve pump mix

Circulating liquid plug
Chamber Valves Fluidic network

valve seat

pressure inlet pneumatic layer elastic membrane fluidic layer

Pref Pa >> Pref

microfluidic path Pref Pa << Pref

Actuation pressure Pref: Reference pressure
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**Cartridge Assembly Line**

- Automated Manufacturing Line
- Reliable assembly and laser welding processes
- Scalable to high-volume manufacturing
- Economy-of-Scales Effects with increasing Production Volumes

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**Laser welding process**

- Cost efficient materials
- Line beam and mask
- Unique material combination

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Potential Use Cases in Oncology

Screening Methods:
- High-risk HPV Infections
- Precancer forms

Companion Diagnostics:
- Patient stratification for targeted Tumor Therapies (MAB’s, Kinase- and Checkpoint-inhibitors)
- Monitoring of targeted Tumor Therapies (eg. early detection of “escape mutations”)
- Periodic reiteration of Automated Tests based on “Liquid Biopsy Samples” at the Point-of-Care

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Companion diagnostics:

- Chronic Myeloid Leukemia (CML)
  - Monitoring of targeted cKIT-Therapy and Status of Chronical Disease

- Non-Small-Cell Lung Carcinoma (NSCLC)
  - Monitoring of targeted EGFR-Tki Therapy (Mutations in EGFR: L858R, DEL19, T790M, ALK)

- Colon Cancer
  - Monitoring of targeted EGFR-MAB Therapy (Mutations in KRAS, BRAF)

- Breast Cancer
  - Monitoring of targeted Therapies (Mutations in HER2, HER3, ER, BRAF…)
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Biopsies in Oncology

**Today**
- Tissue Samples (FFPE*) from Surgery or „Solid Biopsy“
- Patient Stratification: Decision on initial Personalized Treatment from genetic information of Tumor Sample
- Repetitive Biopsies for Therapy Monitoring (if done at all)

**Tomorrow**
- Therapy Monitoring by minimally invasive repetitive „Liquid Biopsies“
- Genetic information on Tumor from CTC’s and/or cfDNA harvested from the blood-stream

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* FFPE = Formalin Fixation Paraffin embedded Tissue

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Tracking of Therapy-relevant Mutations by Liquid Biopsies

**The Game-changer: Lab-on-Chip (LoC)**
- Input to LoC: Patient Blood sample (< 1ml)
- Isolation of cfDNA (reduction of background-DNA)
- Amplification of target-cfDNA (PCR)
- Analyse specific genetic information from the Tumor for changes in therapy-relevant Mutations (?)
- Reiteration at regular time-intervals easily possible: low burden to the patient, fully automated, fast, low-cost
- Adaptation of Treatment whenever necessary

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**LoC for Cancer Therapy Monitoring**
- cfDNA in Patient Blood sample
- Cancer Patient with initially known Mutation Status at start of therapy
- Adaptation of Treatment
- Changes in Mutation status (?)
- Molecular Diagnostics in LoC
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Summary and Outlook

- We developed a flexible Open Platform for the Automation of Complex Diagnostic Workflows
- Integration of a large variety of Molecular Diagnostics assays on disposable Chips
- Driven by the same universal Processing Station, the Vivalytic Analyser
- Offering short time-to-result, low hands-on-time, high multiplex degree, usability at the Point-of-Care
- Scope of Applications: Infectious diseases, Monitoring of Personalized Therapies in Oncology
- Combined with "Liquid Biopsies": CTC's and/or cfDNA harvested from the blood-stream
- From central laboratories to the Point-of-Care

THANK YOU FOR YOUR ATTENTION