STATENS SERUM INSTITUT

Automating the lab for large-scale testing and sequencing

Bart Wilkowski

May 26, 2023

VISION

STATENS SERUM INSTITUT

Statens Serum Institut - an internationally leading research and emergency preparedness organization that enhances the health of humans and animals.

MISSION

STATENS SERUM INSTITUT

We prevent and combat infectious diseases and congenital disorders through research, surveillance, diagnostics, and counseling.

About me: Bartlomiej Wilkowski, PhD., EMBA

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BAW@ssi.dk

Statens Serum Institut (2011-)

- 12/2022 - : Head of department **(Digital Infrastructure)**
- 2020 – 2022: IT section leader (Danish National Biobank & Testcenter Denmark)
- 2017-2020 : IT team leader (Danish National Biobank)
- 2011-2016 : IT system developer - Danish Biobank Register (biobanks.dk)

Technical University of Denmark (2007-2011)

- Research assistant & Ph.d. student - (Biomedical informatics, semantic text mining)

Technical University of Lodz, Poland (2002-2007)

- MSc engineer, International Faculty of Engineering, Telecommunications & Computer Science

Roadmap

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- **Danish National Biobank**
  - Introduction
  - Wet lab data-driven automation
  - Two examples of laboratory workflow optimization
- **Establishment of Testcenter Danmark**
  - Introduction
  - Flows in TCDK
  - Examples of WGS flow tracking
  - Underlying IT architecture
  - Summary
- **Next steps / initiatives**
  - Virus Monitoring at Work project

Danish National Biobank

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- Situated at Statens Serum Institut, a national laboratory for more than 100 years
  - Collections with many (millions) of biological samples
  - Increasing demand from researchers
  - Overview and structure was needed

- Funds were raised to establish
    - Danish Biobank Register (SSI samples and other joining biobanks)
    - National Biobank that offers state-of-the art and well monitored freezing units and laboratory facilities

novo nordisk fonden

Uddannelses- og Forskningsministeriet

LUNDBECKFONDEN

Danish National Biobank

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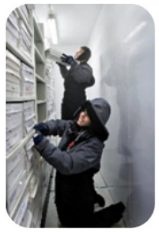
Automated storage

High throughput automation

Manual storage



Total storage capacity: >15M

High throughput analyses

Danish National Biobank - services

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DNA extraction

1200 samples/day
One step conc./normalisation

Genetic analysis

- NGS-500 sequencing
- Array genotyping
- Targeted sequencing
- Mutation analysis
- Methylation
- mRNA microRNA profiling

Metabolomics and proteomics

- Explorative and focused using mass spec.
- LC-tandem mas spec. for small analytes
- MALDI-TOF mass spec.

Immunoassays

- Autoimmune disease diagnostics and development
- Biacore interaction analysis
- Antibody development
- Protein purification, characterization, conjugation
- MesoScale platform 10 analytes/run
- Luminex platform 30-50 analytes/run

Neonatal screening for congenital disorders

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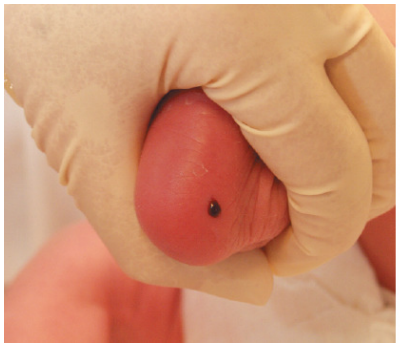
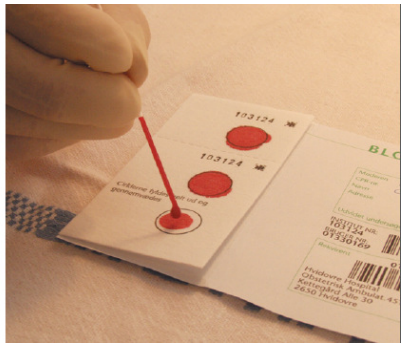
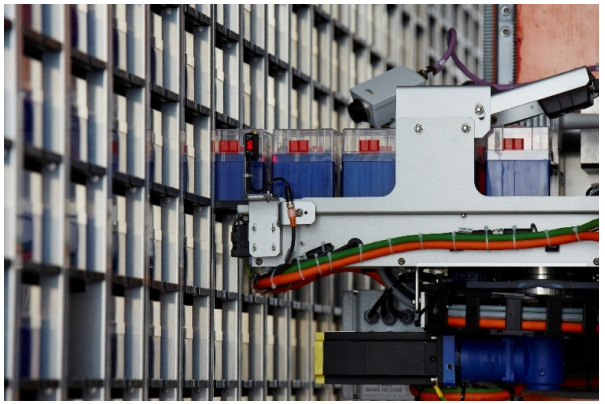
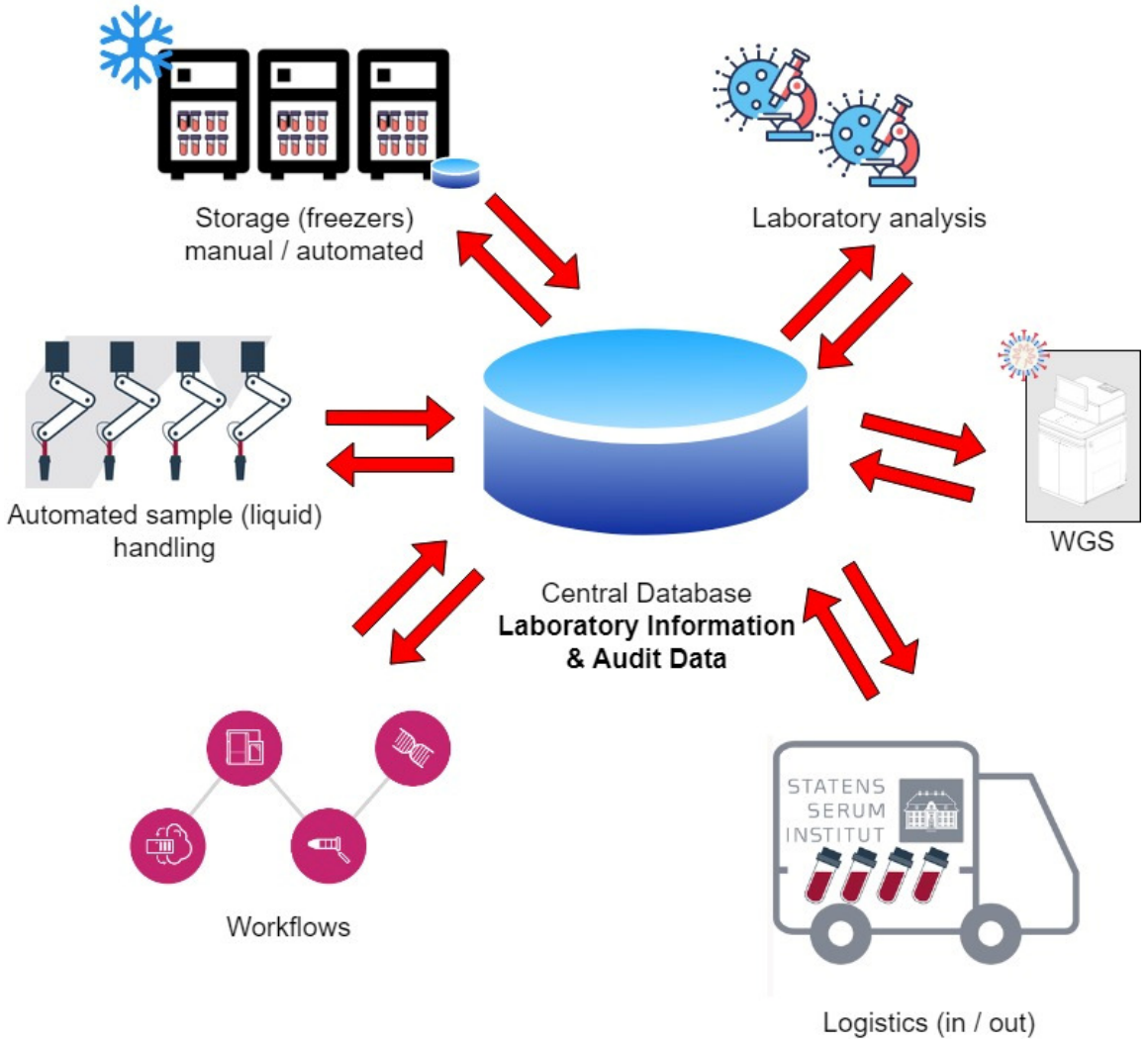
- Manual collection of > 2M Guthrie cards (filter paper) placed in automated -20°C automated freezer







General automated laboratory model



Workflows / laboratory routines

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- **Manual** – sample handling entirely carried out by manually
  - Manual pipetting
  - No lab robots
  - Manual data acquisition, registration & transfer (e.g. handwritten log, manual data registration – Excel?, data transfer on USB sticks between labs, etc.)
  - (-) Hardly scalable, prone to human errors
  - (+) Easy to follow by process operators, excellent for new method development, prototyping

- **Automated** – sample handling processed entirely by automation
  - Liquid handlers (pipetting robots)
  - Automated sample processing robots (e.g. DNA/RNA extraction, sequencing, etc.)
  - Automated data flow (robot – database)
  - (-) Hard to follow by process operators, requires automation expertise to modify processes
  - (+) Easily scalable, repetitive and high processing quality (if properly implemented)

- **Hybrid** – a mix of the two above

Unique part identification & automation

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- Strong requirement for efficient automation / process optimization:
  - Unique codes for every part, tool, element of a workflow (labware)
  - Coded labels
  - Management of codes used (database)
  - Database-controlled batch printing
    - Label printer integration with API

Quick summary of code types

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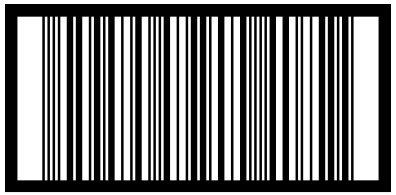
1D barcode (fx EAN)

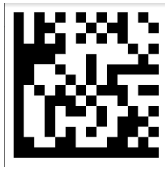


Danish health insurance card / primary care tube

QR code

Coronapass app

Data matrix code



DNB/Testcenter tube

Direct part marking (DPM) is a process to permanently mark parts with product information including serial numbers, part numbers, date codes, and barcodes. This is done to allow the tracking of parts through the full life cycle. The interpretation of 'permanent' often depends on the context the part is used.

Data-driven laboratory management (Danish National Biobank)

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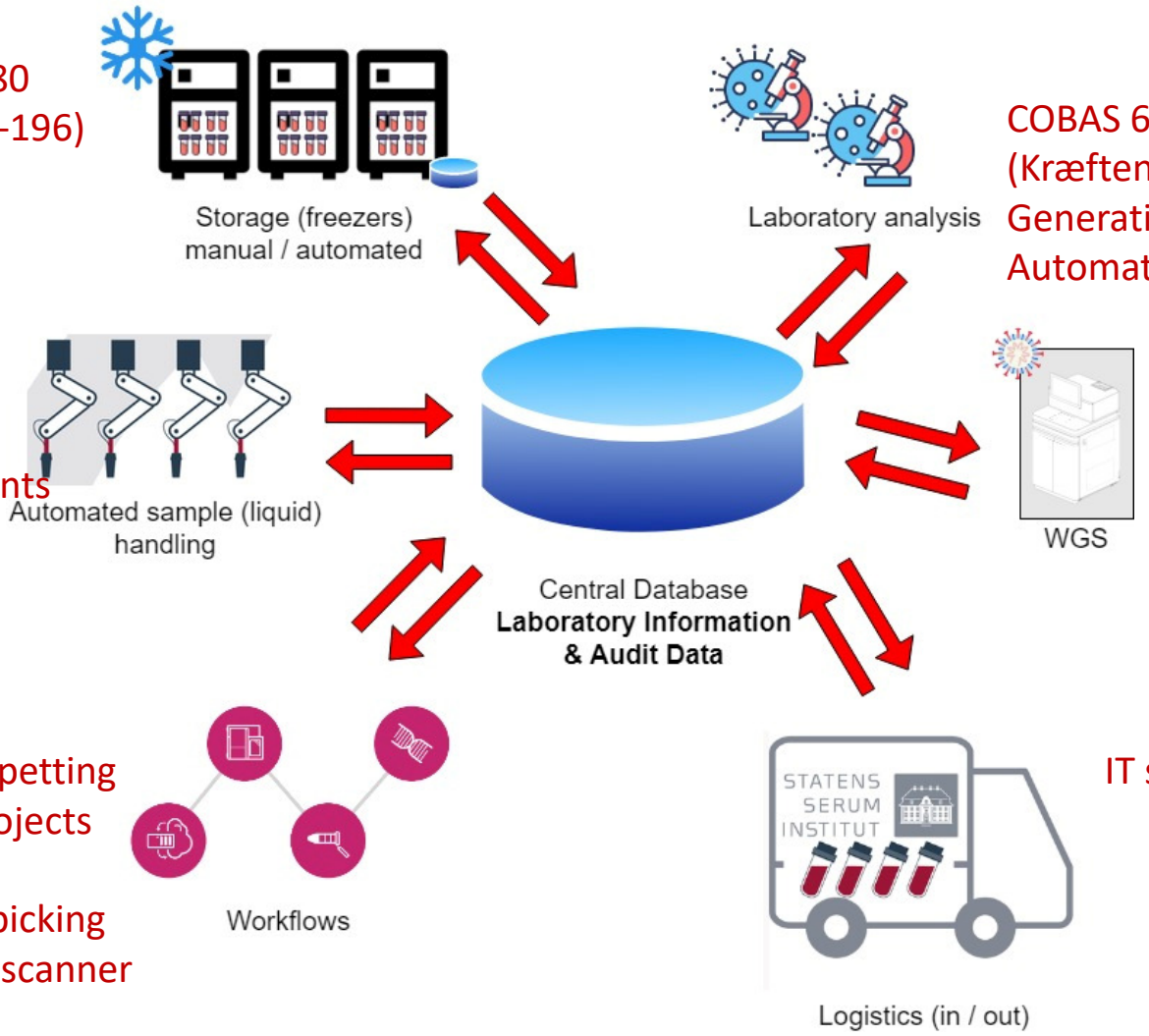
Automated -20/-80
Manual (-20/-80/-196)



COBAS 6000 analyzer
(Kræftens Bekæmpelses Next Generation project)
Automated analysis results data flow

Hamilton:
liquid handler robots
DNA extraction/normalization
DNA concentration measurements

IT-optimized manual pipetting
for specific research projects

Semi-automated tube picking
Mohawk picker + Ziath scanner

IT solution for shipment tracking

Example 1: Optimizing manual pipetting workflow

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- **Before** (manual procedure for a lab technician):
  1. Open Excel file with sample barcodes **approved** for a project (**source list**)
  2. Open Excel file with target plate template (**target list**)
  3. Take first source tube, scan into Excel (source list) to verify that the tube is approved
  4. If tube found, scan it to the other Excel file (target list)
  5. Take target tube, scan into Excel (target list) – same line as the source tube
  6. Do the pipetting
  7. Repeat from Step 3.

Example 1: Optimizing manual pipetting workflow

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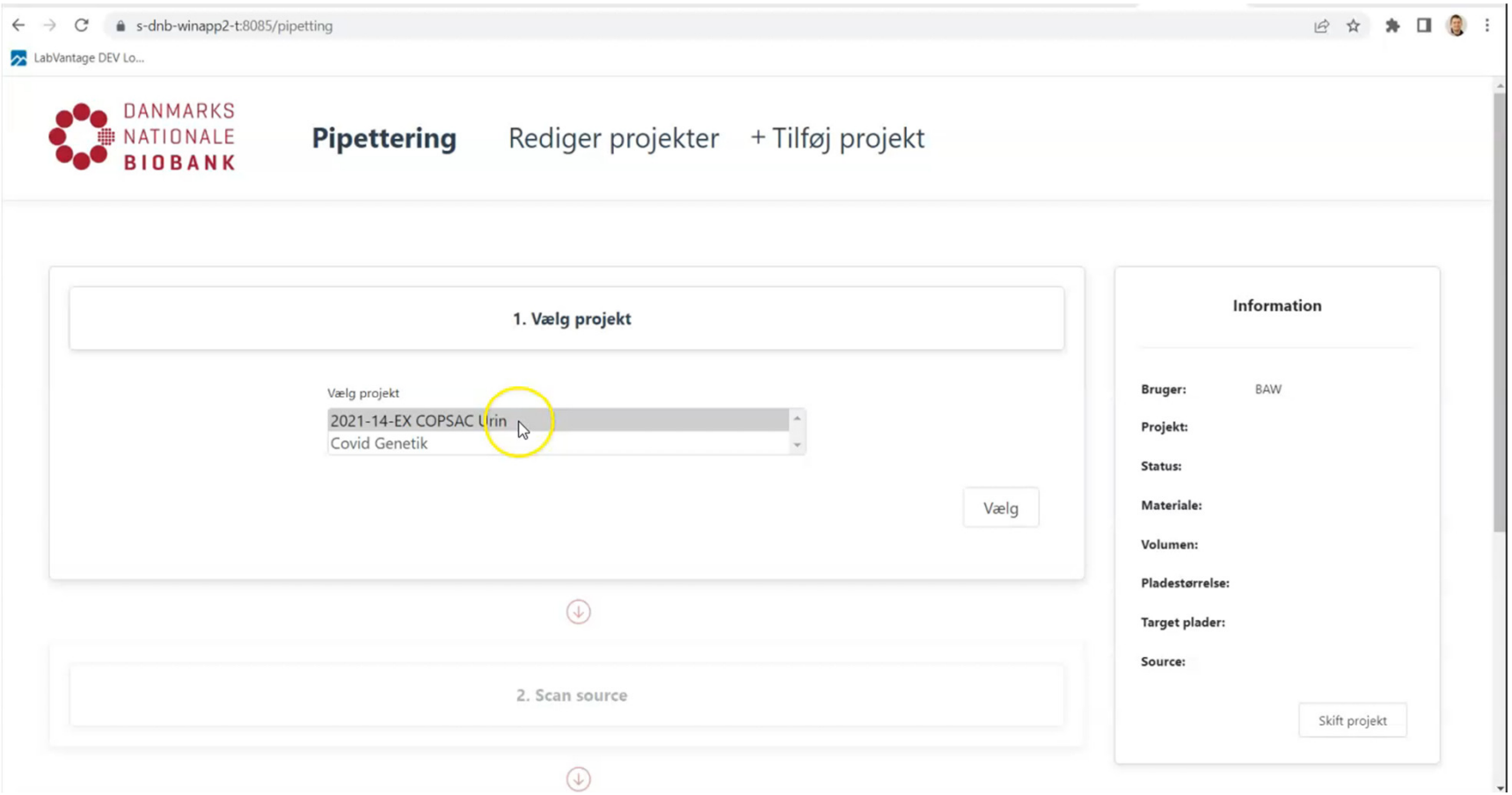
<u>After</u>
(IT-guided flow)

- Web-service solution
- No manual data typing (Excel-free)
- On-the-fly data validation
- Full process tracking/audit (database)



Example 2: Optimizing manual tube picking

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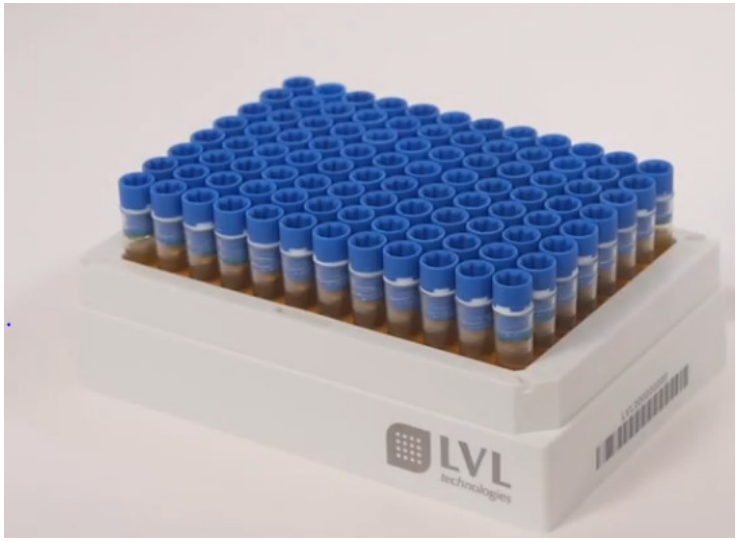
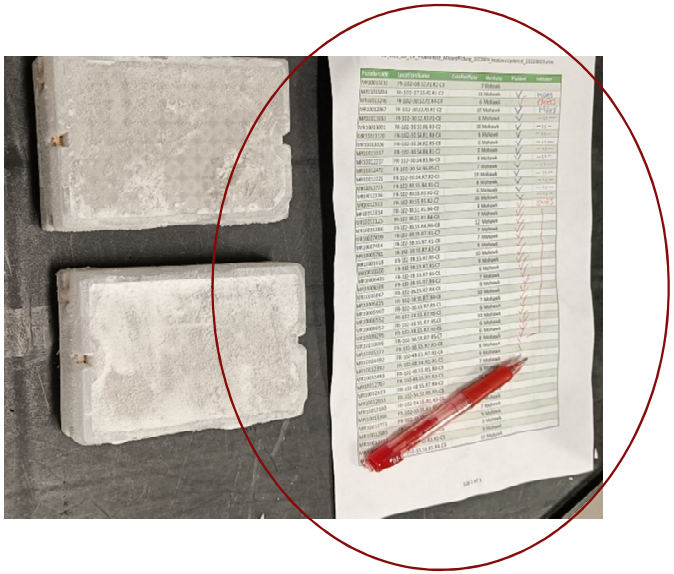
- for each plate,
  - pick the tubes at positions, specified on a paper picklist, using tweezers (pincet)
- double check, after picking, the picked positions with the printed paper picklist.





Example 2: Optimizing manual tube picking

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Establishment of TCDK

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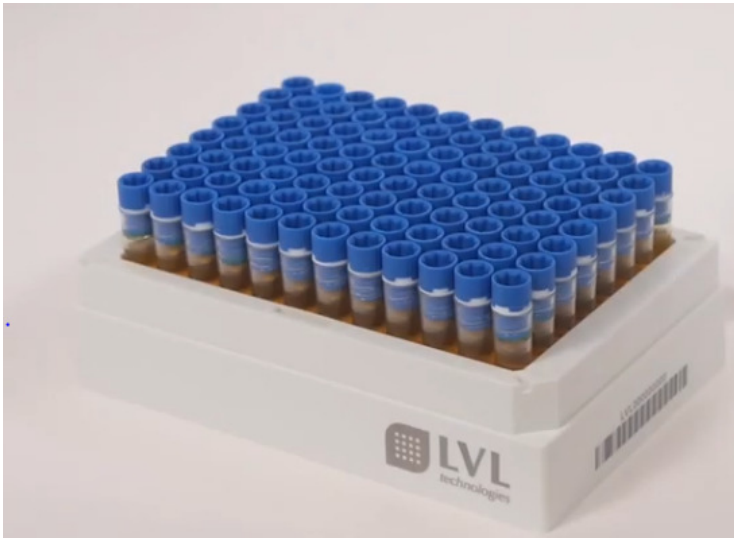
- Late March 2020:
  - Aim: establish national COVID19 testing infrastructure
  - up to 10,000 analyzed swab tests / day
  - Deadline: late April 2020

Requires manual handling

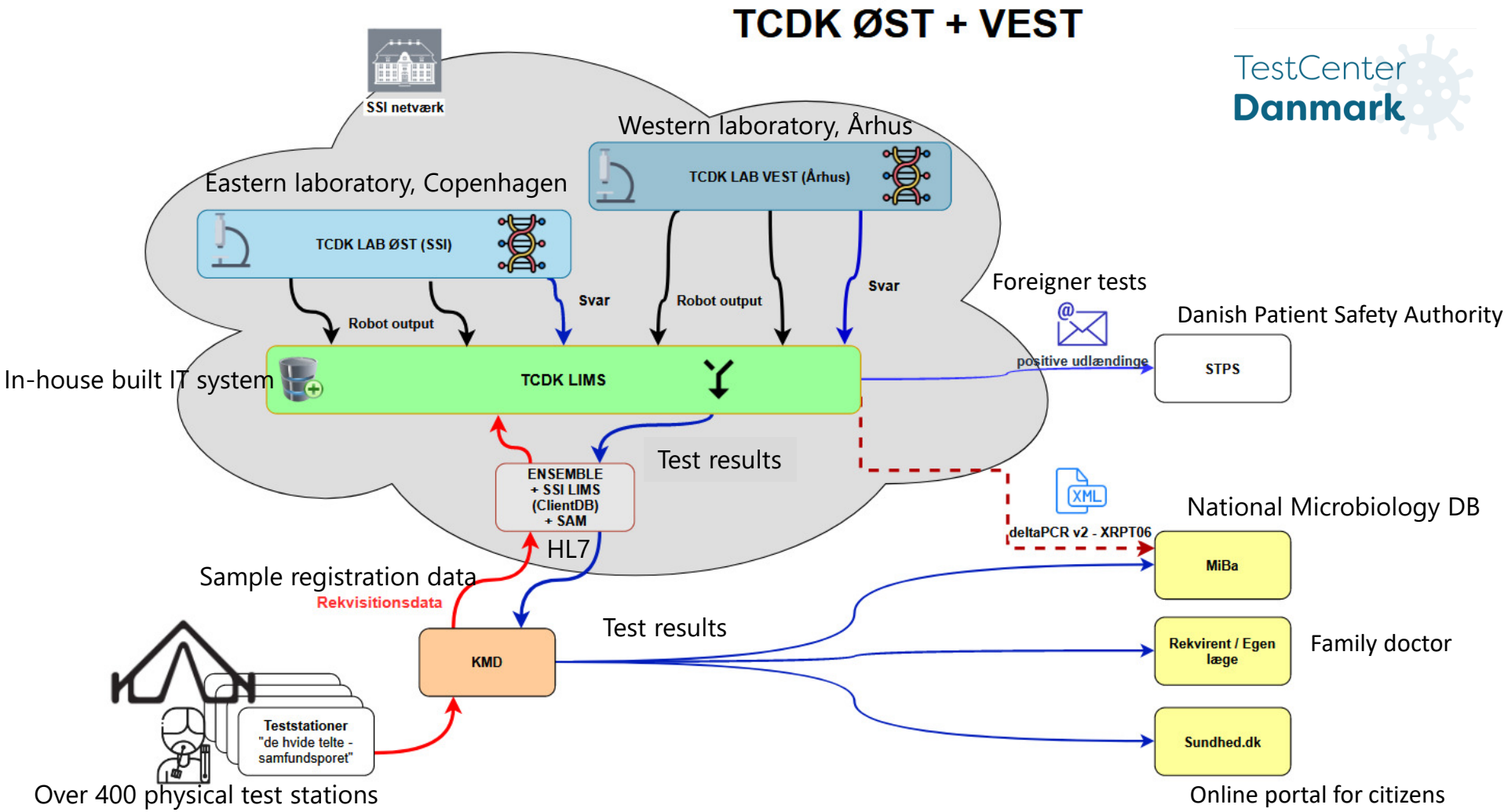
Not scalable

Decision

Use biobank common format



TCDK data flow and architecture



Task: build automated data flow - primary PCR analysis

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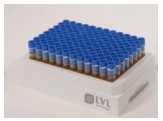
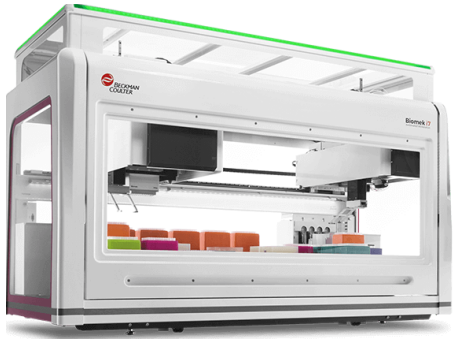
Solution:

based on experiences from the automated solutions
@ Danish National Biobank



Physical plate reception scan

1. Plate/sample (source) scan
2. Add PBS (Phosphate-Buffered Saline)
3. Shake
4. Pipetting to (target) deepwell



1. Plate (source) scan
2. RNA extraction
3. Pipetting to (target) mastermix

1. Plate (source) scan
2. PCR

Plate info

Detaljeret oversigt over en plade

Scan barkode på plade

Påvist:
Inkonklusiv:

Teststation

TCD000133559

(Hovedstaden) Fælledparken - 905373

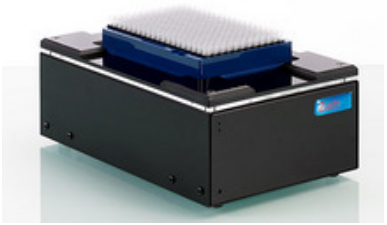
TURISTER (Fælledparken Grænsenær - 150620UL25)

TCD000133559 -> PPBS00140217 -> NULL -> LUIG00028388 (Besvaret)

	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E								F		P↑		
F												P↓
G												X
H												X

Plate overview based on:
- Teststation (sample origin)
- Sample datetime

Picking of positives samples
- Variant PCR
- WGS



TCDK automated flows

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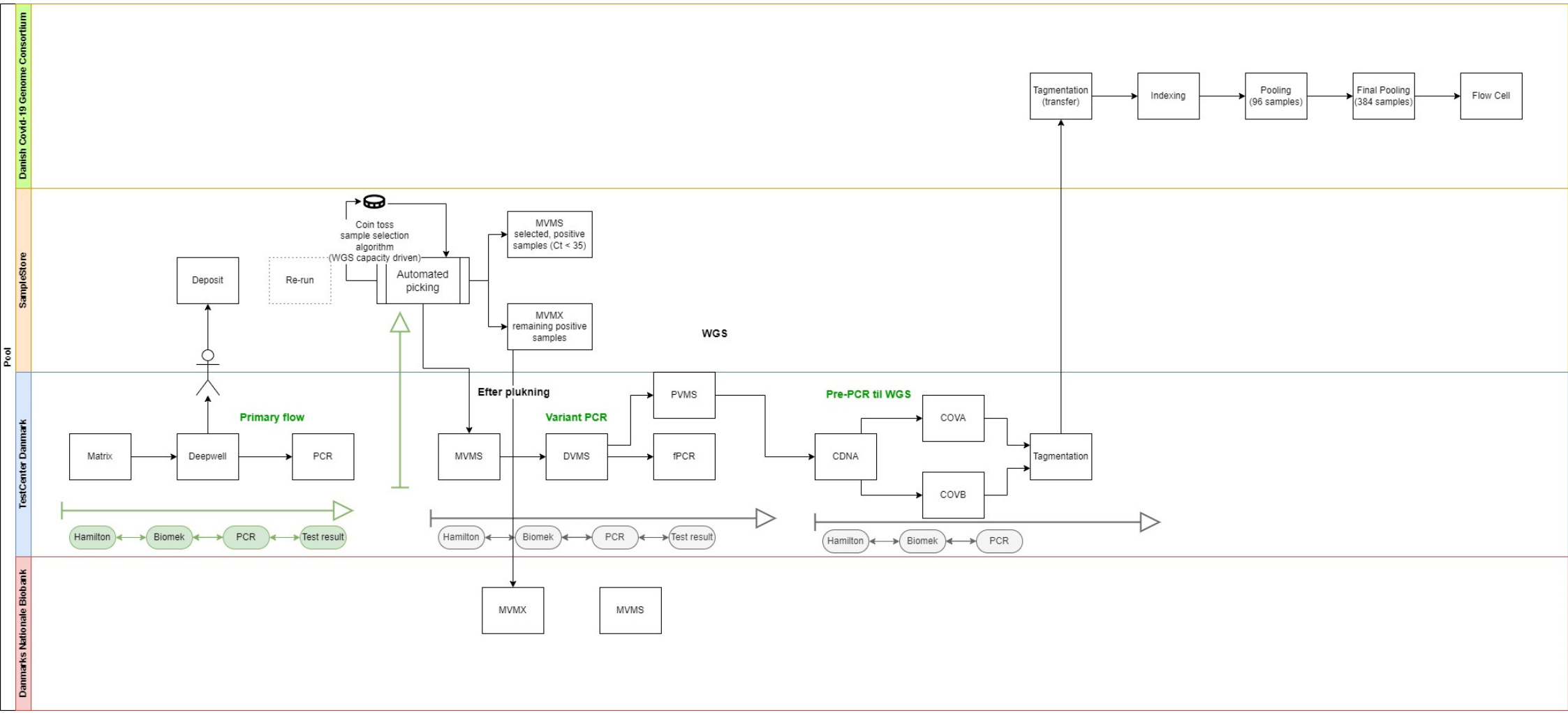

WGS flow tracking (webservice)

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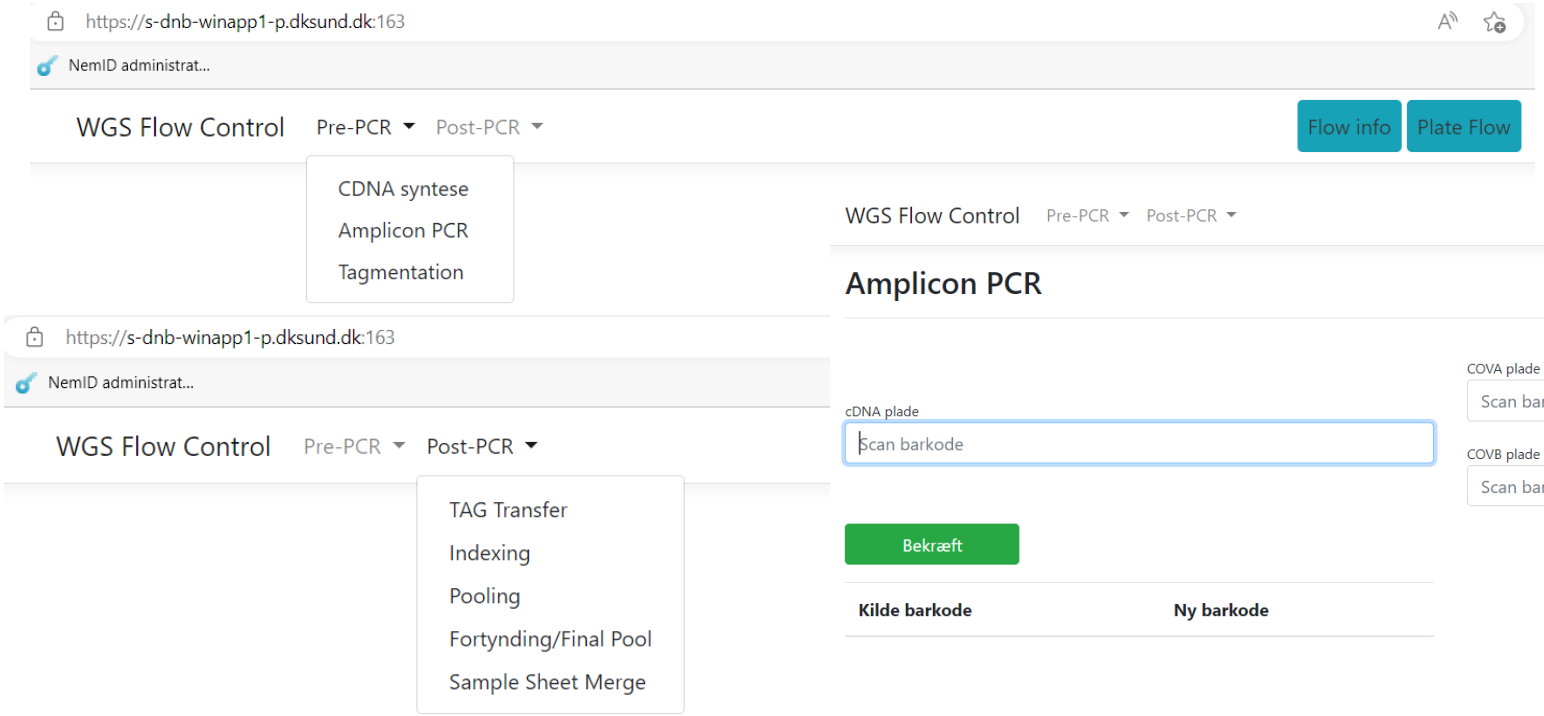

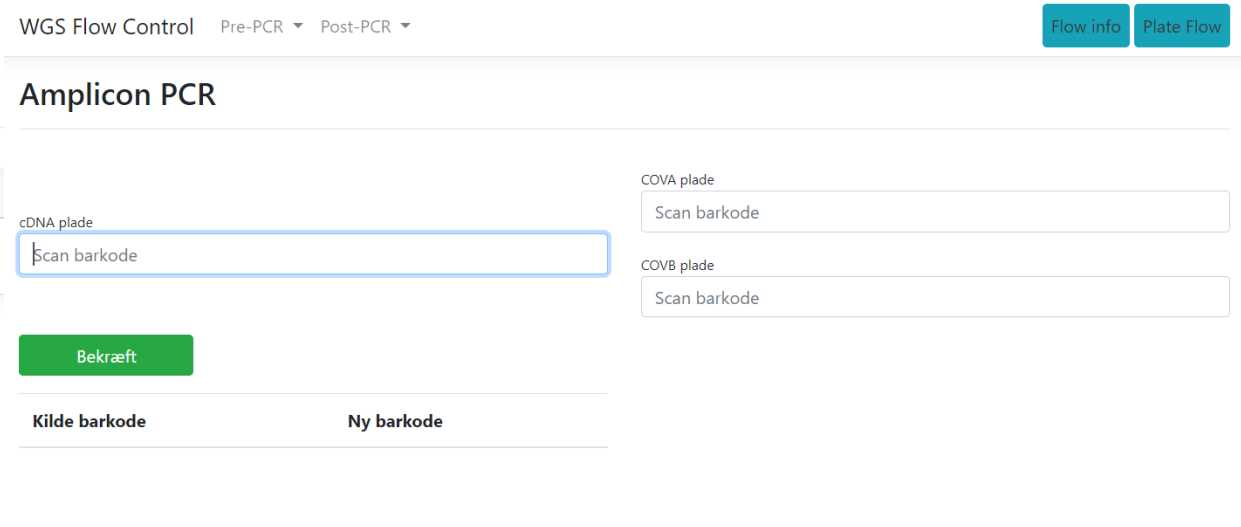

WGS flow tracking (webservice)

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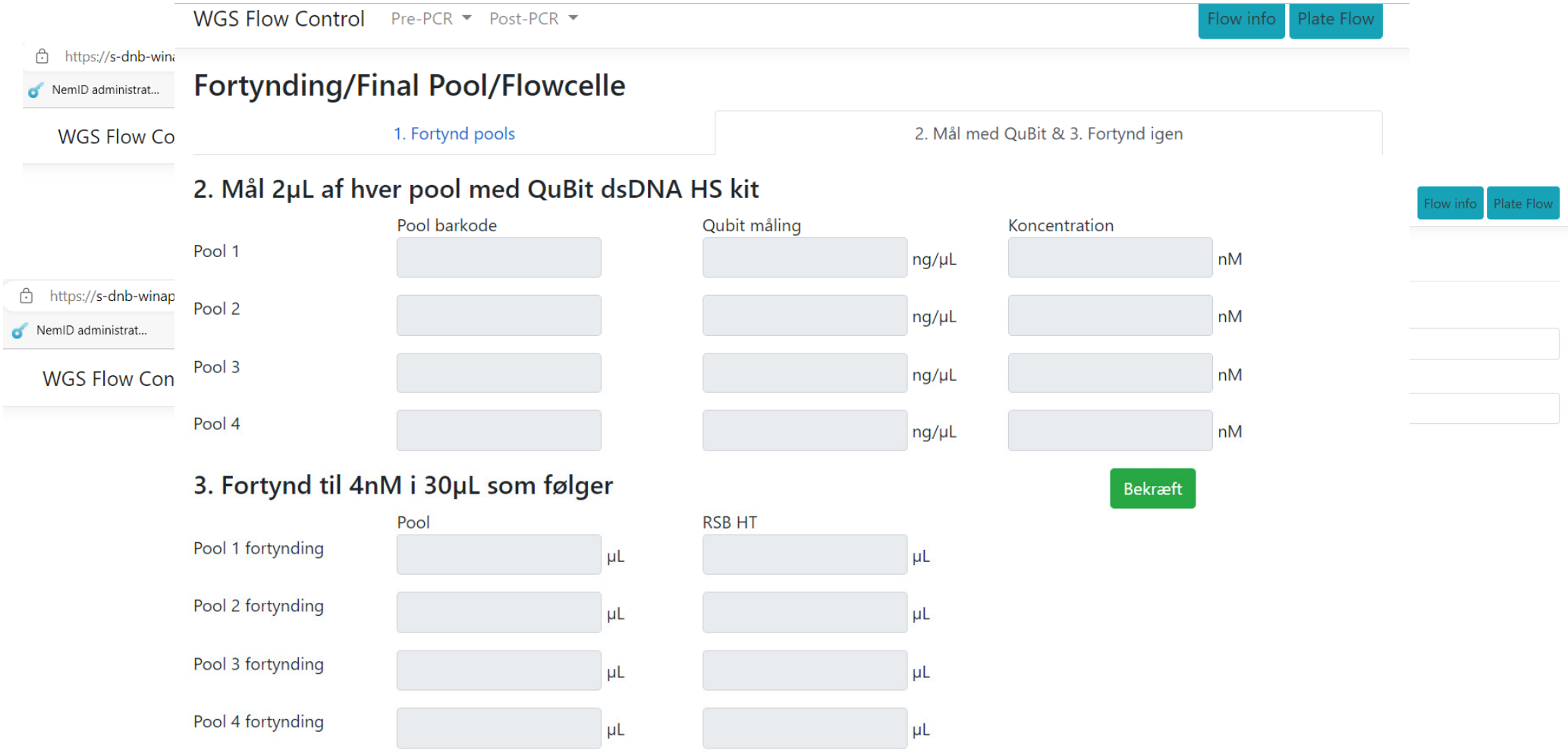

WGS Plate flow

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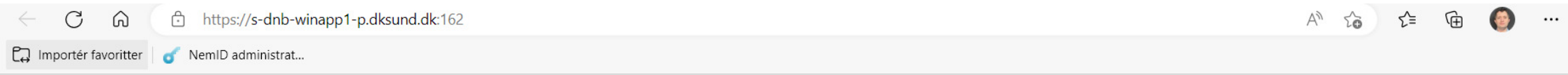

WGS PlateFlow

RNA BC	CDNA BC	COVA BC	COVB BC	TAG BC	TAG2 BC	INDEX BC	Pool BC	Final Pool BC	Flowcelle	VMS Biomek	In
PROJ00000883	CDNA00009772	COVA00008723	COVB00008723	TAG000008214	TAG200017207	A15862591-IDT36	PP002824	FP000804	H7NLWAFX5		25-05-
PROJ00000882	CDNA00009773	COVA00008724	COVB00008724	TAG000008727	TAG200017206	A15849124-IDT35	PP002823	FP000804	H7NLWAFX5		25-05-
PVMS00011515	CDNA00009770	COVA00008722	COVB00008722	TAG000008215	TAG200017204	A15845656-IDT33	PP002821	FP000803	H7T5KAFX5	23-05-2023 11:56:23	25-05-
PVMS00011516	CDNA00009771	COVA00008721	COVB00008721	TAG000008216	TAG200017205	A15849037-IDT34	PP002822	FP000803	H7T5KAFX5	23-05-2023 11:56:23	25-05-
PVMS00014711	CDNA00009774	COVA00008552	COVB00008552	TAG000008726	TAG200017199	15801247-IX01		FP000801	H7T2LAFX5	16-05-2023 12:03:10	19-05-
PVMS00014712	CDNA00009775	COVA00008554	COVB00008554	TAG000008728	TAG200017203	15843546-IX04		FP000802	H7NMJAFX5	15-05-2023 10:53:50	19-05-
PVMS00014713	CDNA00009784	COVA00008553	COVB00008553	TAG000008724	TAG200017201	15789187-IX02		FP000802	H7NMJAFX5	15-05-2023 10:53:50	19-05-
PVMS00014712	CDNA00009783	COVA00008556	COVB00008556	TAG000008719	TAG200017200	15793651-IX01		FP000802	H7NMJAFX5	15-05-2023 10:53:50	19-05-
PVMS00014713	CDNA00009782	COVA00008555	COVB00008555	TAG000008725	TAG200017202	15825451-IX03		FP000802	H7NMJAFX5	15-05-2023 10:53:50	19-05-

WGS Flow Control

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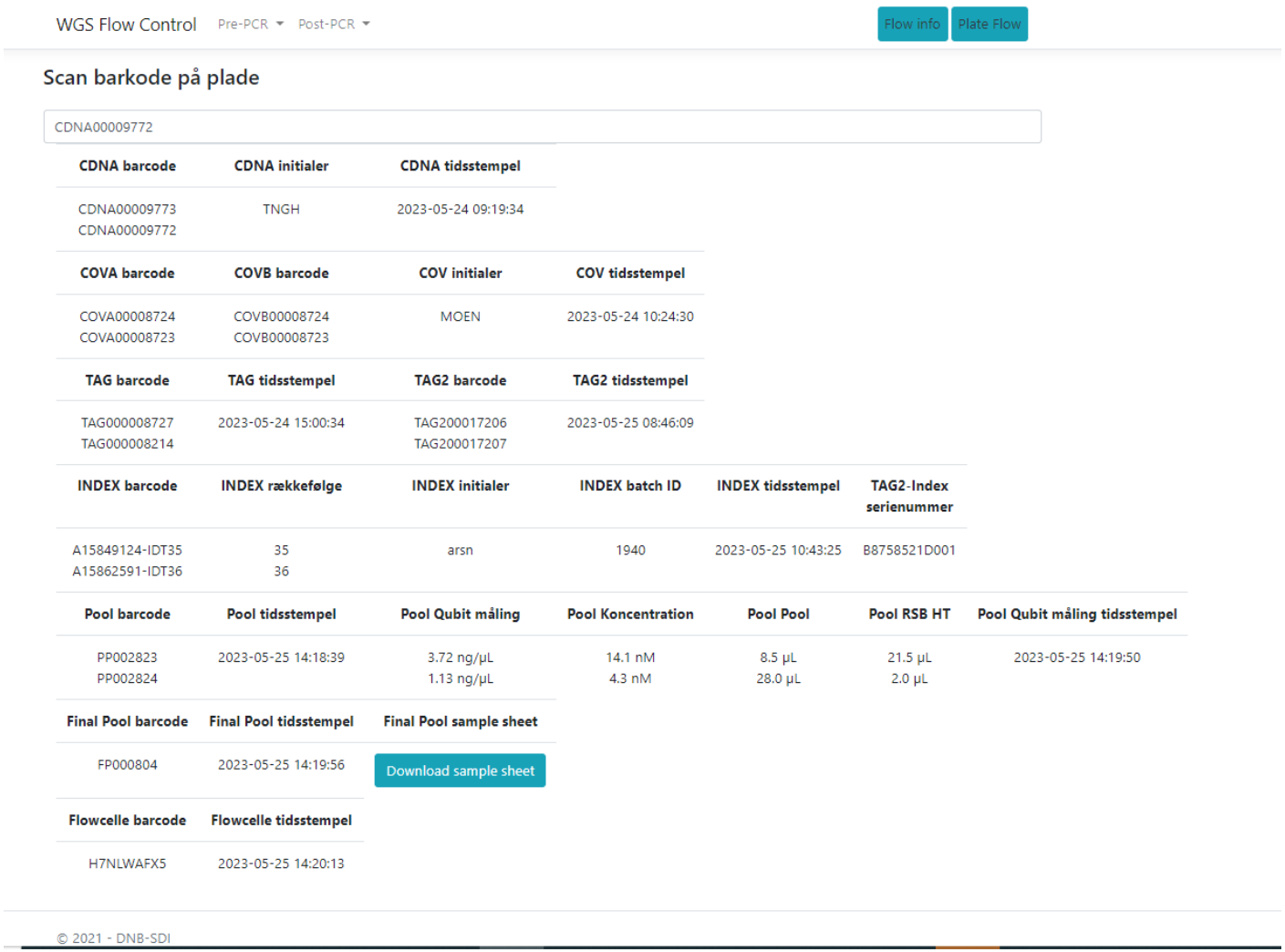

WGS Flow Control Pre-PCR Post-PCR Flow info Plate Flow

Scan barkode på plade

CDNA00009772

CDNA barcode	CDNA initialer	CDNA tidsstempel
CDNA00009773 CDNA00009772	TNGH	2023-05-24 09:19:34

COVA barcode	COVB barcode	COV initialer	COV tidsstempel
COVA00008724 COVA00008723	COVB00008724 COVB00008723	MOEN	2023-05-24 10:24:30

TAG barcode	TAG tidsstempel	TAG2 barcode	TAG2 tidsstempel
TAG000008727 TAG000008214	2023-05-24 15:00:34	TAG200017206 TAG200017207	2023-05-25 08:46:09

INDEX barcode	INDEX rækkefølge	INDEX initialer	INDEX batch ID	INDEX tidsstempel	TAG2-Index serienummer
A15849124-IDT35 A15862591-IDT36	35 36	arsn	1940	2023-05-25 10:43:25	B8758521D001

Pool barcode	Pool tidsstempel	Pool Qubit måling	Pool Koncentration	Pool Pool	Pool RSB HT	Pool Qubit måling tidsstempel
PP002823 PP002824	2023-05-25 14:18:39	3.72 ng/µL 1.13 ng/µL	14.1 nM 4.3 nM	8.5 µL 28.0 µL	21.5 µL 2.0 µL	2023-05-25 14:19:50

Final Pool barcode	Final Pool tidsstempel	Final Pool sample sheet
FP000804	2023-05-25 14:19:56	Download sample sheet

Flowcelle barcode	Flowcelle tidsstempel
H7NLWAFX5	2023-05-25 14:20:13

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DANMARKS NATIONALE BIOBANK

TestCenter Danmark

Underlying IT architecture

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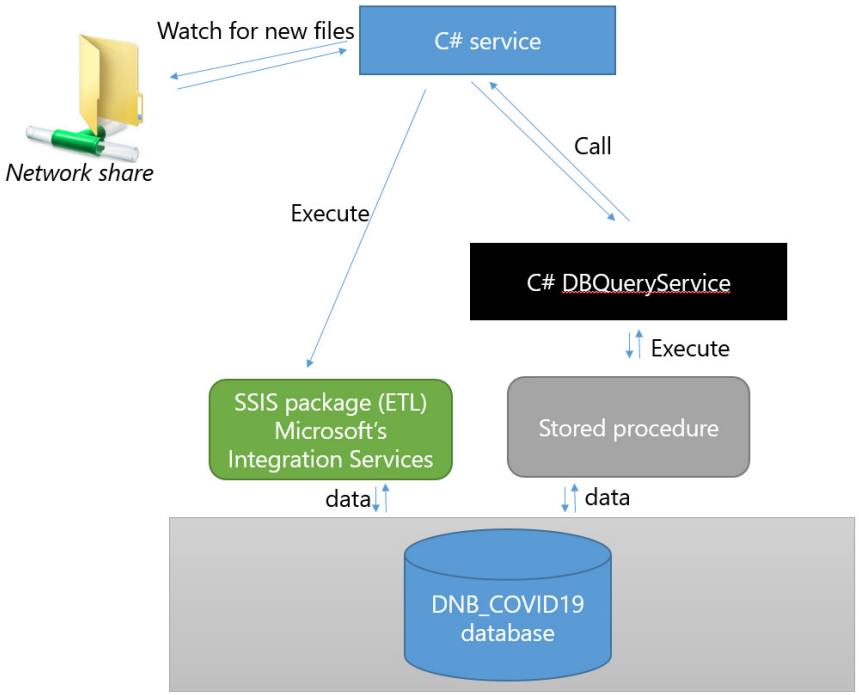
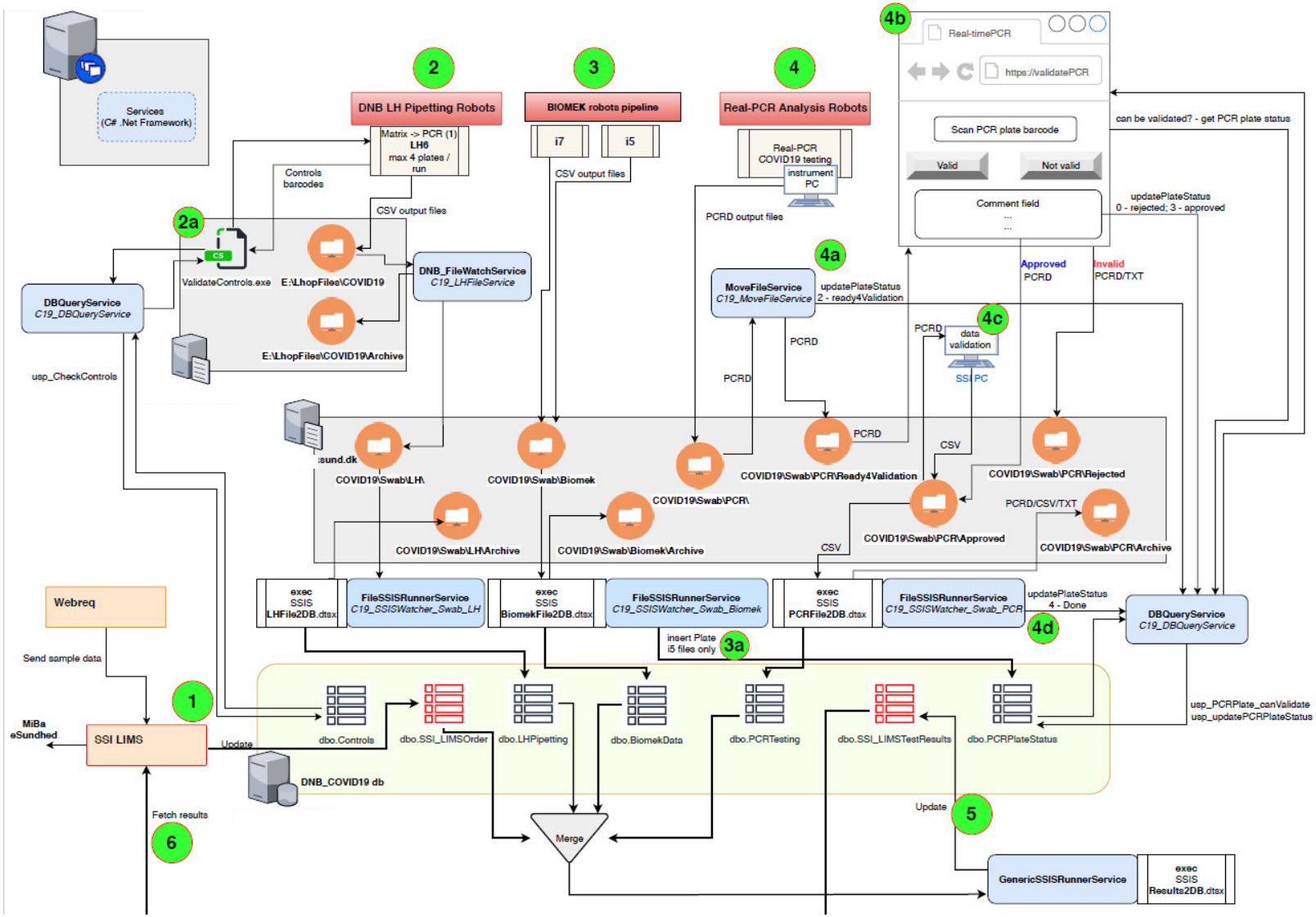
IT service template



- A network of independent services performing different tasks = supporting a single activity in the process flow, e.g.

surveillance / file watch / archiving / reporting / notifications / etc.


Services
(C# .Net Framework)
2
DNB LH Pipetting Robots
3
BIOMEK robots pipeline
4
Real-PCR Analysis Robots
4b
Real-timePCR
https://validatePCR
Scan PCR plate barcode
Valid
Not valid
Comment field
can be validated? - get PCR plate status
updatePlateStatus
0 - rejected; 3 - approved
Matrix -> PCR (1)
LH6
max 4 plates / run
Controls barcodes
CSV output files
i7
i5
CSV output files
Real-PCR COVID19 testing
instrument PC
PCRD output files
2a
ValidateControls.exe
E:\LhopFiles\COVID19
DNB_FileWatchService
C19_LHFileService
E:\LhopFiles\COVID19\Archive
DBQueryService
C19_DBQueryService
usp_CheckControls
4a
MoveFileService
C19_MoveFileService
updatePlateStatus
2 - ready4Validation
Approved
PCRD
Invalid
PCRD/TXT
4c
data validation
SSI PC
PCRD
CSV
sund.dk
COVID19\Swab\LH\
COVID19\Swab\Biomek
COVID19\Swab\PCR\Ready4Validation
COVID19\Swab\PCR\Rejected
COVID19\Swab\PCR\
COVID19\Swab\PCR\Approved
PCRD/CSV/TXT
COVID19\Swab\LH\Archive
COVID19\Swab\Biomek\Archive
COVID19\Swab\PCR\Archive
exec SSIS LHFile2DB.dtsx
FileSSISRunnerService
C19_SSISWatcher_Swab_LH
exec SSIS BiomekFile2DB.dtsx
FileSSISRunnerService
C19_SSISWatcher_Swab_Biomek
exec SSIS PCRFile2DB.dtsx
FileSSISRunnerService
C19_SSISWatcher_Swab_PCR
updatePlateStatus
4 - Done
4d
DBQueryService
C19_DBQueryService
Webreq
Send sample data
insert Plate
i5 files only
3a
1
MiBa
eSundhed
SSI LIMS
Update
dbo.Controls
dbo.SSI_LIMSOrder
dbo.LHPipetting
dbo.BiomekData
dbo.PCRTesting
dbo.SSI_LIMSTestResults
dbo.PCRPlateStatus
usp_PCRPlate_canValidate
usp_updatePCRPlateStatus
DNB_COVID19 db
Fetch results
6
Merge
Update
5
GenericSSISRunnerService
exec SSIS Results2DB.dtsx

DANMARKS NATIONALE BIOBANK

TestCenter Danmark

IT infrastructure / data flow

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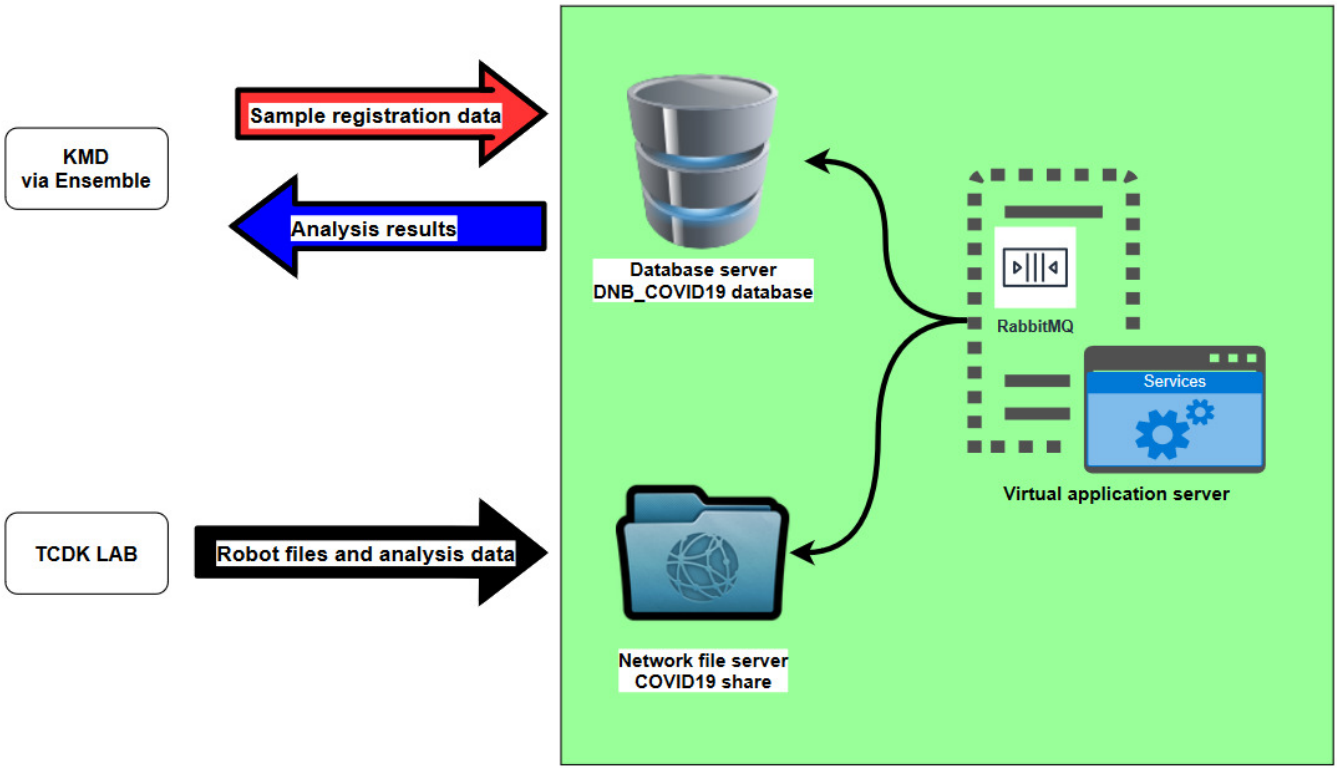
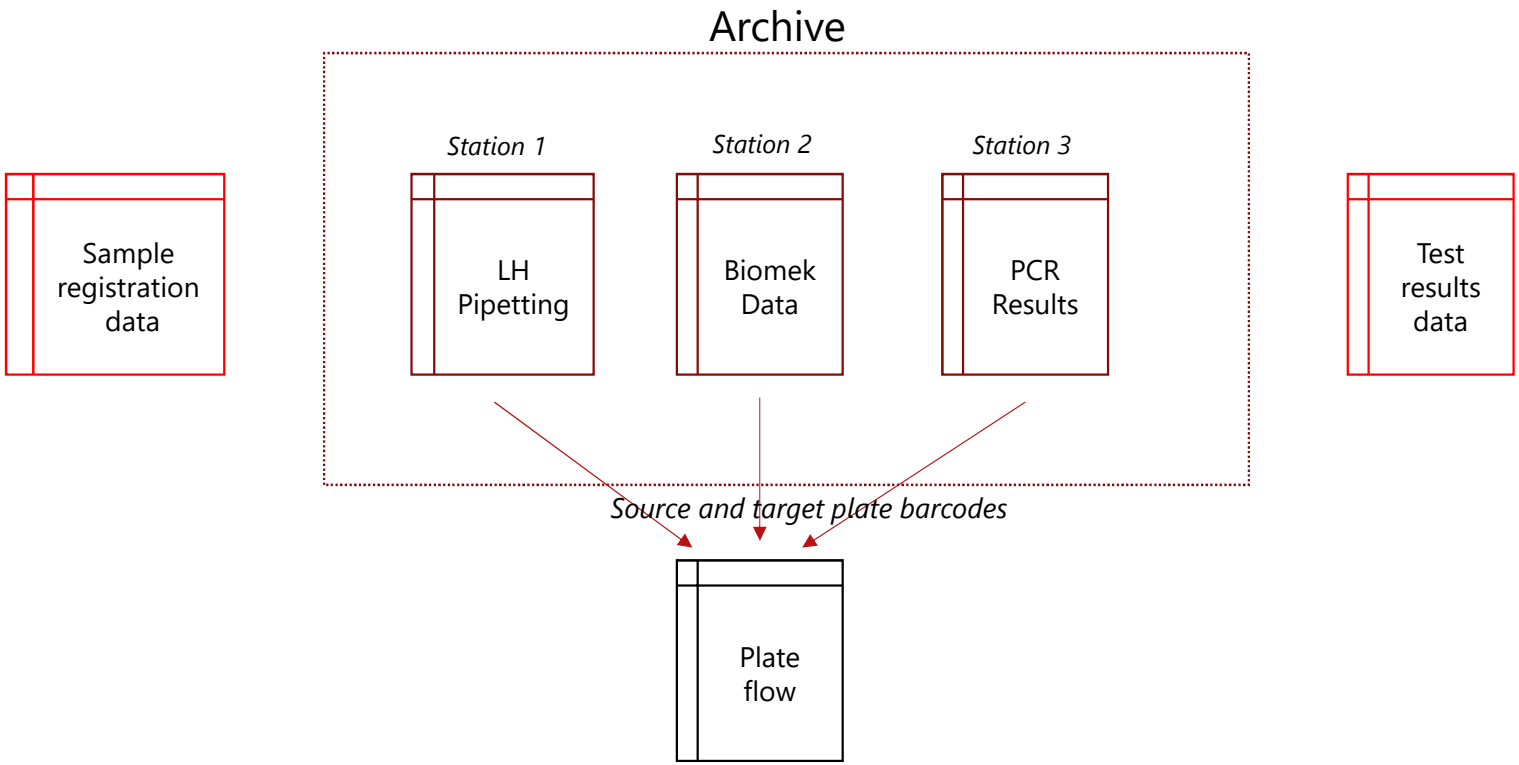


Database model (simplified)



- *linkage between source and target plates*
- *process overview*
- *timestamps for each stations*

From 20k to 225k tests/day

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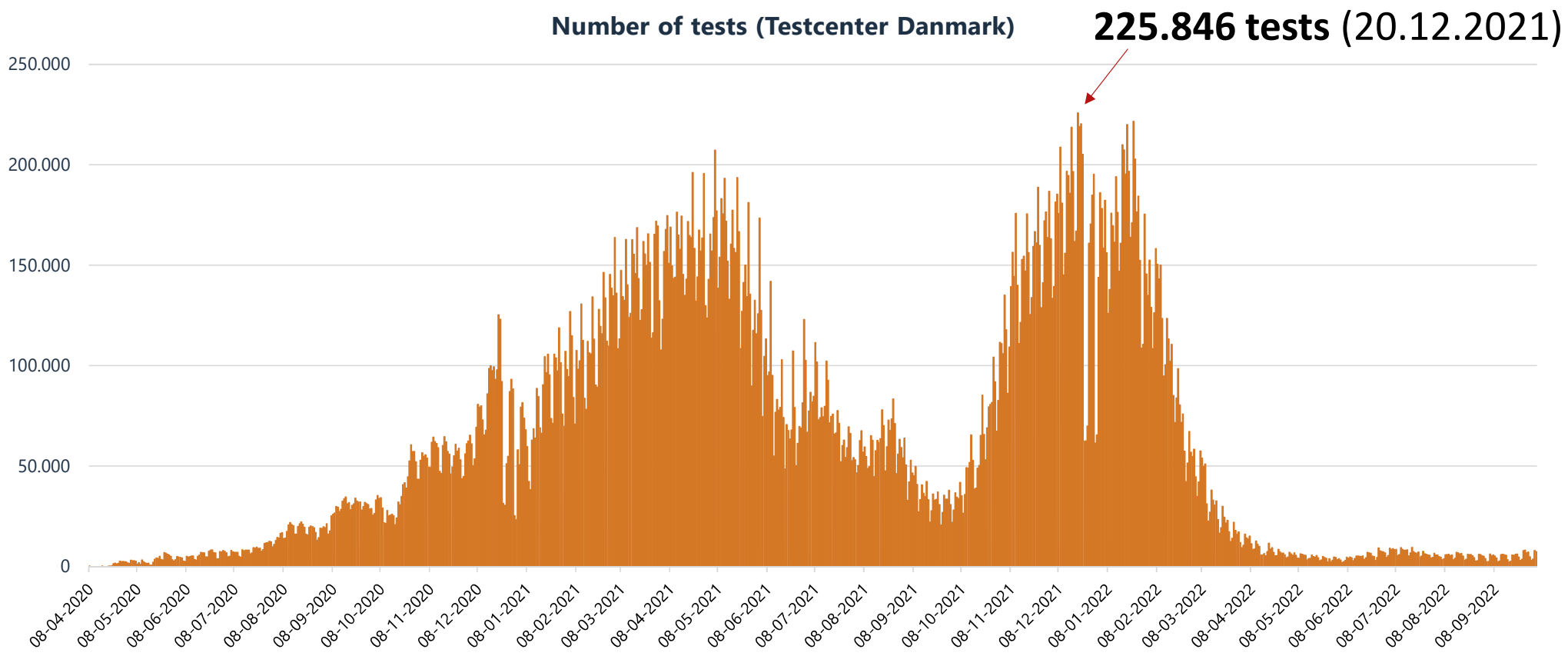

Integration with the Danish National Biobank

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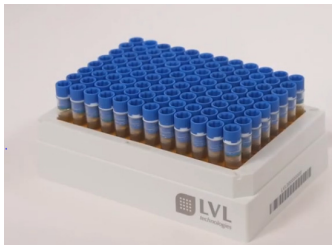
Processed & answered swab tubes (RT-PCR)



Throat swab samples (all positive and 1M negative)

Processed & answered serum tubes (RT SARS-CoV-2 RBD serology)

Blood: (all samples)

Testcenter Denmark infrastructure for biobank projects

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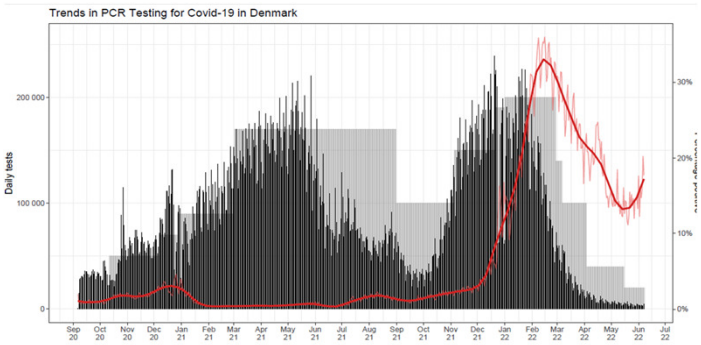
TestCenter Danmark

- Capacity: 200.000 analyses/daily, RNA/DNA extraction
- Quality: ISO accredited flow,
  - Automated sample tracking
  - Semi-automated results release & validation
- Study design & project management
- Pipetting robots & PCR machines
  - 24 Hamilton Star & Vantage
  - 43 Biomek i7
  - 200 Bio-Rad thermal cyclers
- Automated storage system at +4 °C for picking of COVID19+
- Now (after COVID): **offers to take in diverse projects from biobanks**



Roadmap

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- **Danish National Biobank**
  - Introduction
  - Wet lab data-driven automation
  - Two examples of laboratory workflow optimization
- **Establishment of Testcenter Danmark**
  - Introduction
  - Flows in TCDK
  - Examples of WGS flow tracking
  - Underlying IT architecture
  - Summary
- **Next steps / initiatives**
  - Virus Monitoring at Work project

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TCDK App -

registration of **supervised** and **unsupervised** testing

DANMARKS NATIONALE BIOBANK

- Responsive web application
- Supports digital registration of self tests
  - Incl. scanning module for barcodes, QR and **data matrix** codes
- Integration with national citizen identification system
  - digital login - MitID
- Integration with the National Service Platform (NSP)
  - Digital exchange of data and communication for healthcare
  - Parents can register on behalf of their kids (U15)
- Digital registration and consent to research/sentinel projects
- Supervisor management module (for project administrators)
- Access to laboratory results (registered via TCDK App)
- Flexible questionnaire module
- Direct integration with the servers at Statens Serum Insititut

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TCDK App & Virus Monitoring at Work project

DANMARKS NATIONALE BIOBANK

- Start: 1. april 2023
- Aim: To better monitor, prevent and fight infectious diseases
- (SARS-COV-2, Influenza, RS virus)
- Participants: Voluntary employees + household
  - @ Statens Serum Institut
- Expansion plans (Q3-Q4 2023)
  - Include other Danish companies & organizations
  - Planned capacity: 2000 tests / week
- Samples saved in Danish National Biobank
- Virus Monitoring at Work (ssi.dk)

Thank you!

TestCenter Danmark

DANMARKS NATIONALE BIOBANK

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Main sponsor

novo nordisk fonden