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Poland

Treatment of patients with various tick-borne diseases from the whole country

- **OPUS – National Science Centre** - Comprehensive analysis of factors determining the course and clinical consequences of tick-borne encephalitis

- **SONATA-BIS - National Science Centre** - Using multiomics studies to assess the metabolic consequences of tick-borne diseases

- Łuczaj W., Moniuszko-Malinowska A., Domingues P., Domingues R., Gińdzieńska-Sieśkiewicz E., Skrzydlewska E. 2018 Method of diagnosing Lyme disease, method of differential diagnosis of Lyme disease, **lysophosphatidyl-ethanolamine for use as a biomarker,** kit for the diagnosis of Lyme disease and a kit for differential diagnosis of arthritis in Lyme disease. **Patent Office of the Republic of Poland** 17P42226PLOO(PT-66)
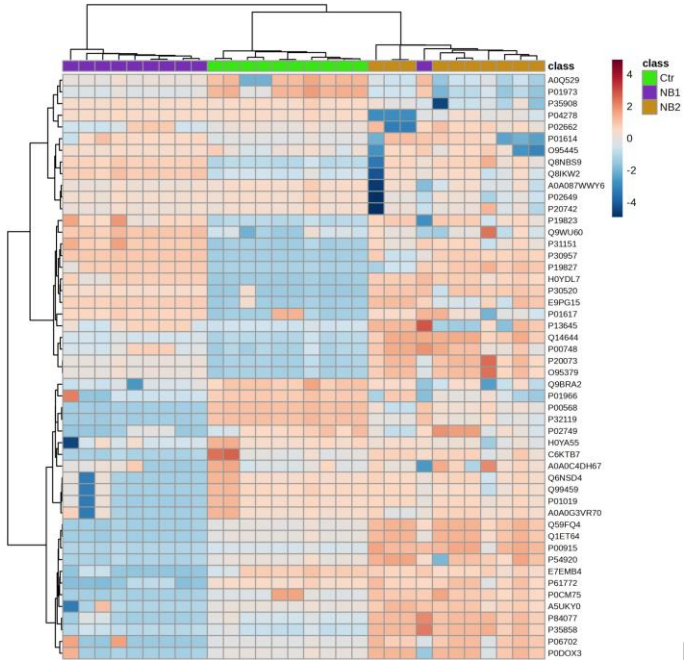
Some results

Figure 4. Heatmap and clustering of 50 top modified proteins indicated in serum of neuroborrelisosis patients (before and after therapy (NB1 and NB2), n=10) comparing to control group (Ctr, n=10).
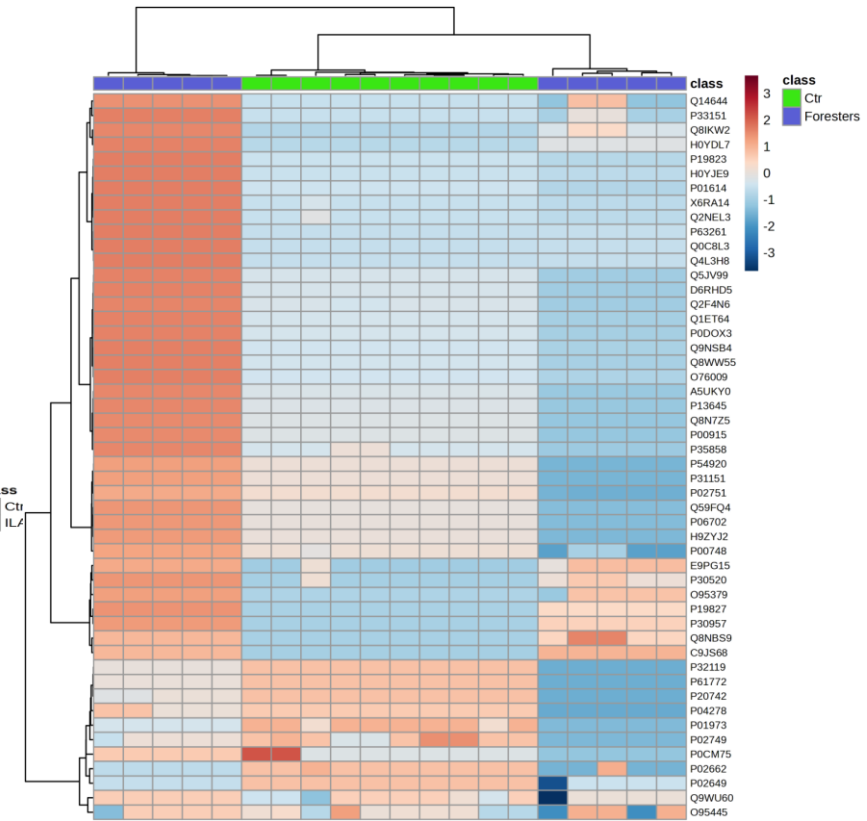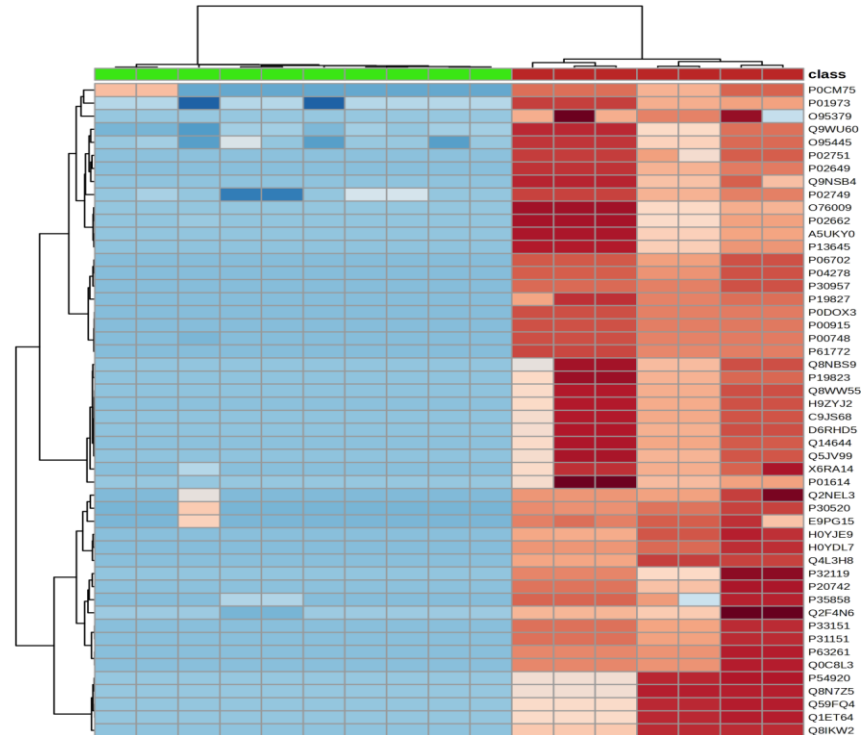
Figure 8. Heatmap and clustering of 50 top modified proteins indicated in serum of forestry men (Foresters, n=10) comparing to control group (Ctr, n=10).

Assessment of the impact of access to testing of TBE in Poland
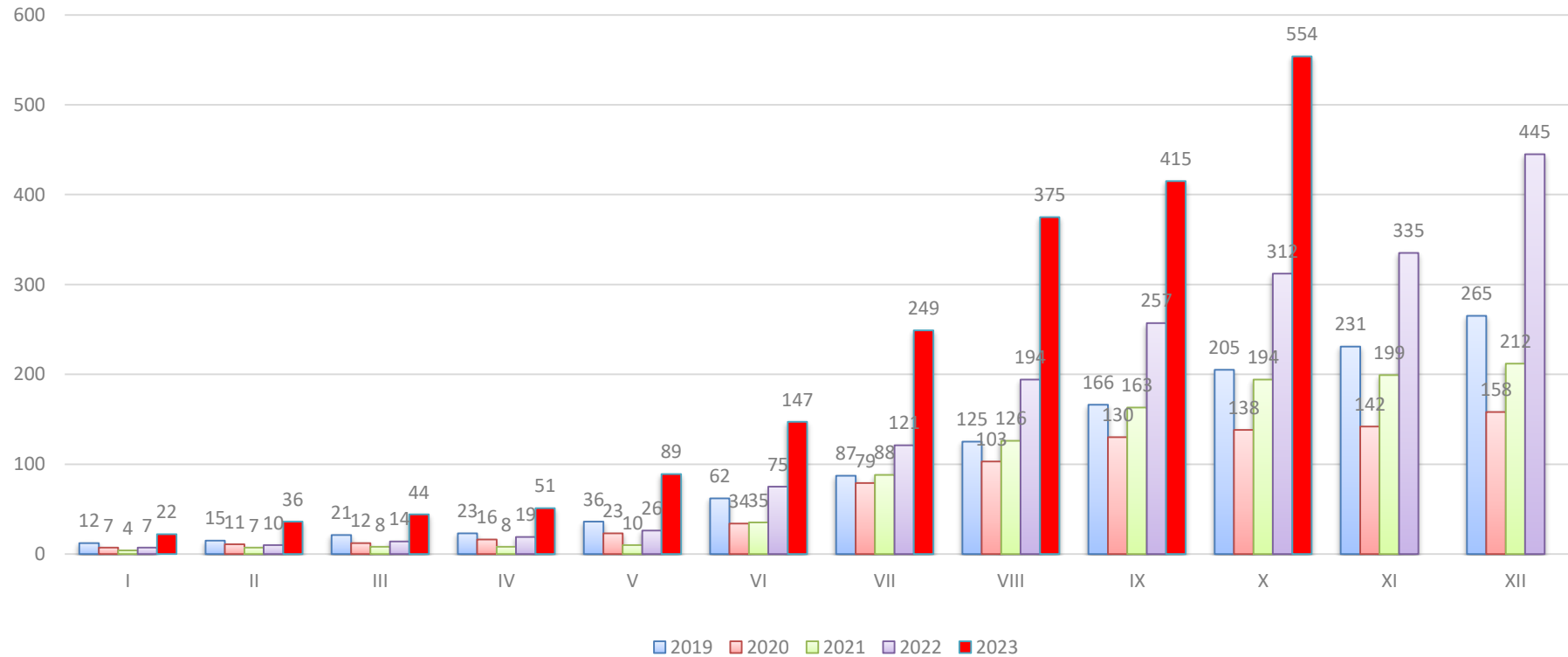
TBE cases in Poland

AIM

- Assessment of the impact of implementing TBE virus infection tests in routine diagnostics of patients with neuroinfections of unknown viral etiology for the identification of TBE virus infections in areas considered non-endemic

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Laboratory UMB

Confirmed cases

n=621, 92(+)

liczba pacjentów   liczba pacjentów +

Legend (left map):
- < 1.0
- 1.1 - 5.0
- 5.1 - 10.0
- 10.1 - 20.0
- > 20.0

Right map values:
3.0%
7.5%
2.0%
17.0%
15.2%
33.0%
17.3%
24.1%
31.0%
17.1%
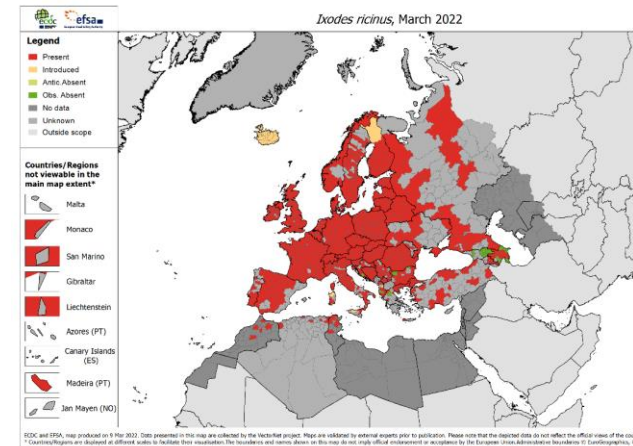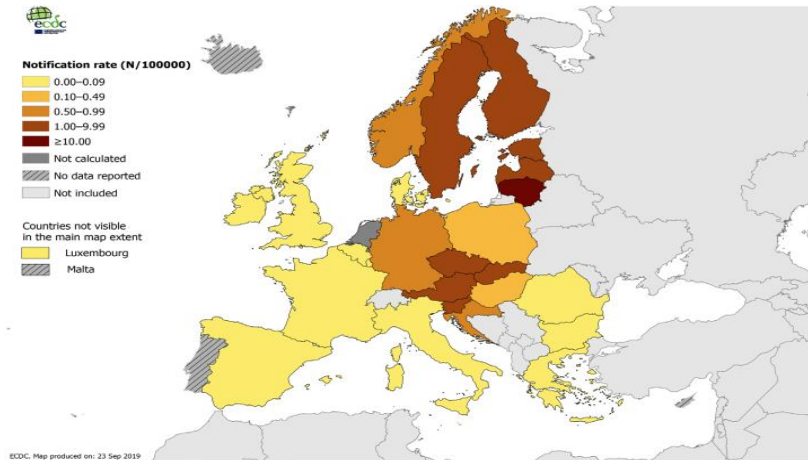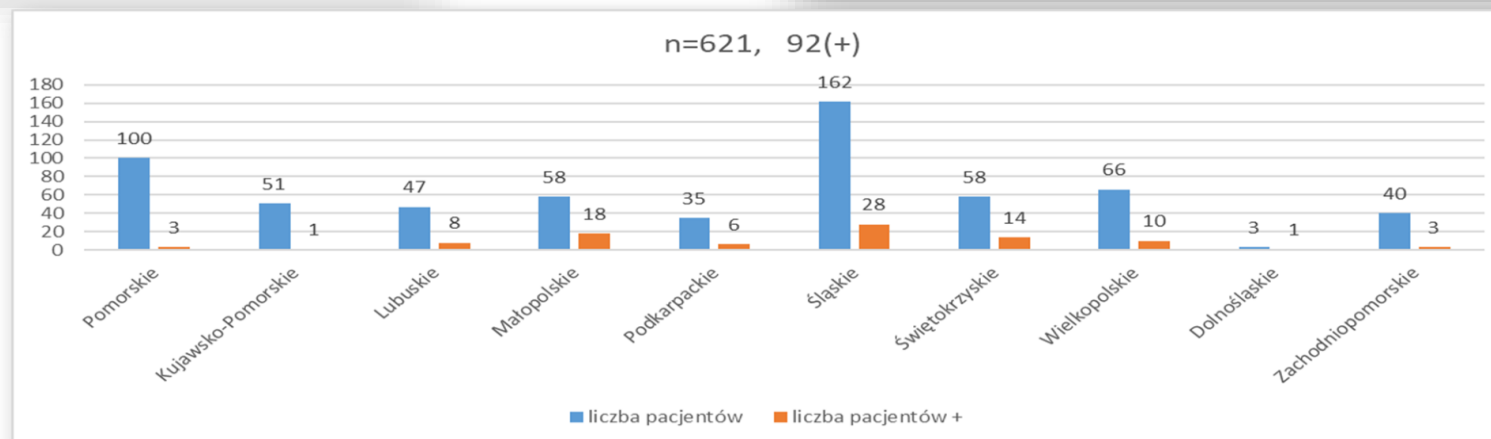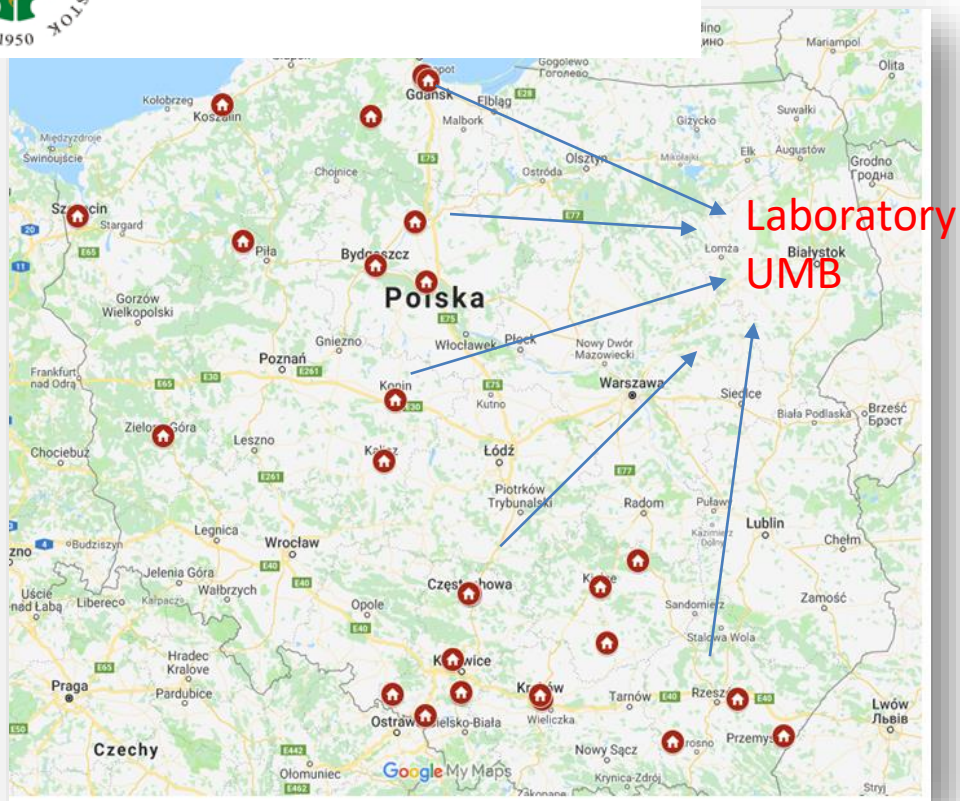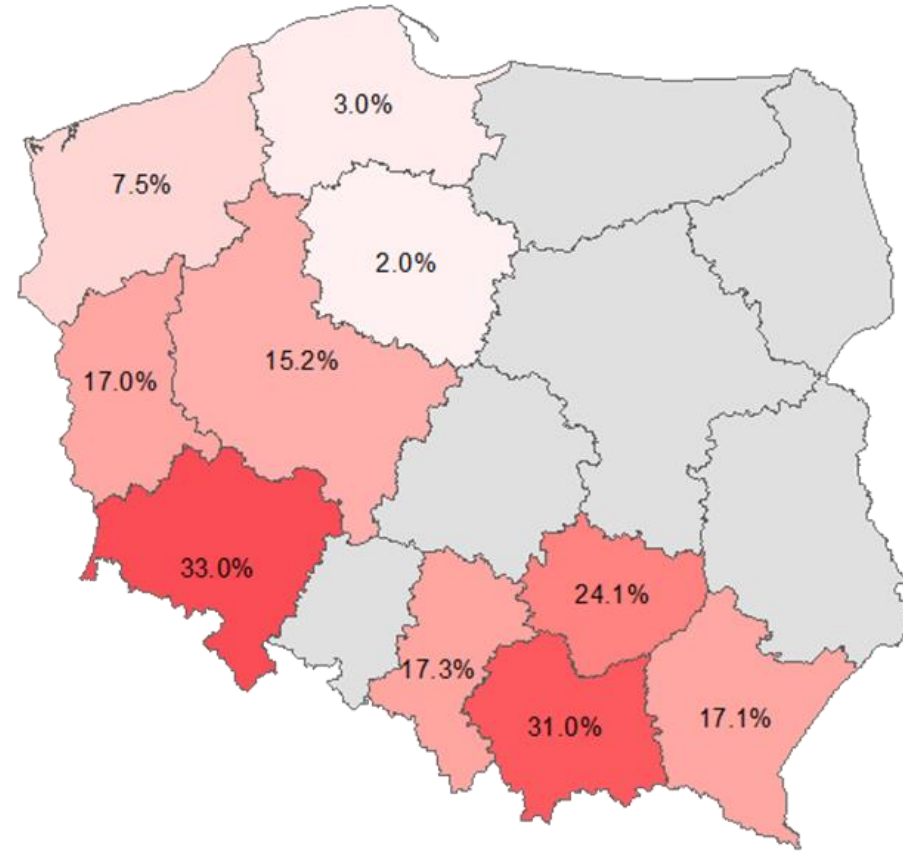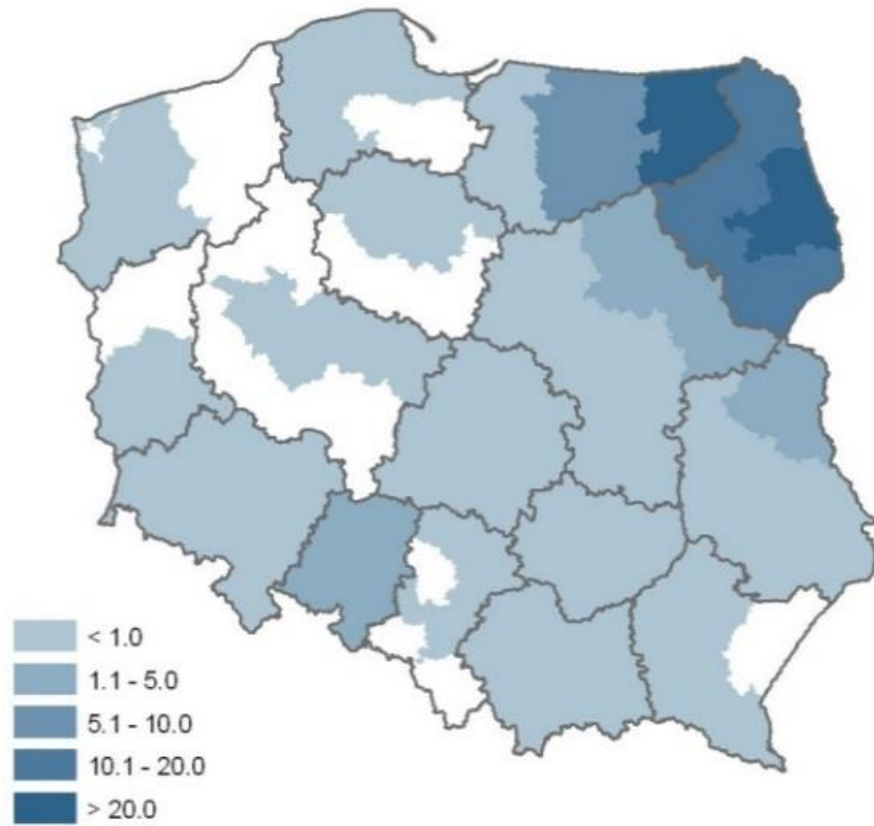
BOLD (Burden of Lyme Disease)
Epidemiological study of potential cases of Lyme disease

Objectives:

- To assess the prevalence and severity of persistent symptoms, as well as quality of life and healthcare resource utilization associated with

- To assess the proportion of suspected Lyme disease cases by clinical presentation who subsequently develop persistent clinical disease symptoms

BOLD

- 469 individuals, 249 women and 220 men

- LD slightly more common in women (54% vs. 46% in men)

- Age distribution similar to surveillance data from other studies - peak in the middle age

	Suspected LD Cases by Final Clinical Diagnosis (N=144)			Controls (Nᵃ=325)	All Subjects (Nᵃ=469)
	Lyme Disease (Nᵃ=93)	Non-Lyme Disease (Nᵃ=36)	Missing Diagnosis (Nᵃ=15)		
	nᵇ (%)	nᵇ (%)	nᵇ (%)	nᵇ (%)	nᵇ (%)
Age (Years)					
0-14	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
15-19	2 (2.2)	2 (5.6)	0 (0.0)	2 (0.6)	6 (1.3)
20-24	3 (3.2)	2 (5.6)	0 (0.0)	19 (5.8)	24 (5.1)
25-29	3 (3.2)	1 (2.8)	1 (6.7)	14 (4.3)	19 (4.1)
30-34	4 (4.3)	4 (11.1)	0 (0.0)	13 (4.0)	21 (4.5)
35-39	6 (6.5)	3 (8.3)	3 (20.0)	26 (8.0)	38 (8.1)
40-44	7 (7.5)	5 (13.9)	0 (0.0)	21 (6.5)	33 (7.0)
45-49	11 (11.8)	2 (5.6)	1 (6.7)	28 (8.6)	42 (9.0)
50-54	6 (6.5)	5 (13.9)	2 (13.3)	40 (12.3)	53 (11.3)
55-59	12 (12.9)	8 (22.2)	2 (13.3)	53 (16.3)	75 (16.0)
60-64	12 (12.9)	1 (2.8)	3 (20.0)	35 (10.8)	51 (10.9)
65-69	8 (8.6)	0 (0.0)	1 (6.7)	29 (8.9)	38 (8.1)
70-74	13 (14.0)	1 (2.8)	0 (0.0)	27 (8.3)	41 (8.7)
75-79	4 (4.3)	1 (2.8)	0 (0.0)	9 (2.8)	14 (3.0)
>=80	2 (2.2)	1 (2.8)	2 (13.3)	9 (2.8)	14 (3.0)
Mean (SD)	54.0 (16.14)	46.4 (16.07)	54.7 (16.65)	52.3 (15.70)	52.3 (15.90)
Median (Q1,Q3)	57.0 (42.0, 67.0)	47.0 (34.5, 56.0)	55.0 (38.0, 64.0)	54.0 (41.0, 63.0)	54.0 (41.0, 63.0)
Min, max	16, 83	15, 87	26, 86	16, 88	15, 88

Preliminary Results from the Burden of Lyme Disease (BOLD) study
a Prospective Active Surveillance Study at Primary Care Practices in Endemic Regions of Six European Countries

MEDICAL UNIVERSITY OF BIALYSTOK

Loew-Baselli A[1], Halsby K[2], Pilz A[1], Stark J[3], Angulo FJ[3], Berglund JS[4], Cibik V[5],
Dybova L[6], Moniuszko-Malinowska A[7], Weimer J[8], Strle F[9], Zakova D[10],
Edwards J[3], Bowdery M[11], Valluri S[12], Gessner B[3], Begier E[13]

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BACKGROUND

- Lyme borreliosis (LB) is the most frequently reported tick-borne disease in Europe, though its incidence is not well characterized.[1]

- Incidence estimates are highly variable across countries. In approximately 70–80% of patients in Europe, LB presents with erythema migrans, a common skin manifestation.[2] Cases of disseminated disease present with more severe manifestations, such as neuroborreliosis and Lyme arthritis.

- To prepare for a global efficacy trial for a candidate LB vaccine, we conducted prospective active surveillance at 13 selected European primary care practices in LB endemic areas of 6 countries.

Figure 1. Study site map

(Each star represents a study site)

METHODS

- All suspected LB cases identified from the primary care practice panel (i.e. the population receiving health care from the site) was documented on a screening log by each site. All newly diagnosed LB was recorded, along with clinical manifestations and standard of care Lyme diagnostic tests results, if available.

- In the initial 12-month phase, all suspected LB cases were offered enrollment. After informed consent, cases were enrolled and interviewed, and their medical records reviewed.

- A final clinical diagnosis was assigned based on the BOLD case definitions (modeled after the European Union Concerted Action on Lyme Borreliosis [EUCALB][3] definition) (Table 1), and clinical manifestations were documented.

- Study samples were tested with modified two-tiered testing to identify laboratory-confirmed LB cases.

- Sites reported their practice panel size and historical LB case count by month (2019-20), allowing annualization of measured 2021 case counts and a projected 2021 LB incidence.
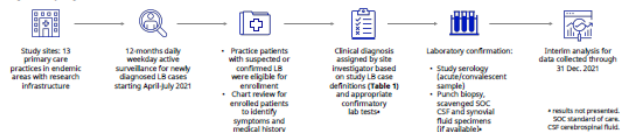
Figure 2. Study design overview

Study sites: 13 primary care practices in endemic areas with research infrastructure → 12-months daily weekday active surveillance for newly diagnosed LB cases starting April-July 2021 → Practice patients with suspected or confirmed LB were eligible for enrollment; Chart review for enrolled patients to identify symptoms and medical history → Clinical diagnosis assigned by site investigator based on study LB case definitions (Table 1) and appropriate confirmatory lab tests• → Laboratory confirmation: Study serology (acute/convalescent sample); Punch biopsy, scavenged SOC CSF and synovial fluid specimens (if available)• → Interim analysis for data collected through 31 Dec. 2021

• results not presented.
SOC standard of care.
CSF cerebrospinal fluid.

Table 1. LB clinical case definitions[3]

Presentation	Signs/Symptoms (at least one)	Laboratory confirmation (at least one)	
		All	Specific for presentation
Erythema migrans	Characteristic red or bluish-red patch, with or without central clearing		•Positive PCR/Culture of Bbsl from skin biopsy
Borrelial lymphocytoma	Painless bluish-red nodule or plaque, usually on ear lobe, ear helix, nipple or scrotum		•Positive PCR/Culture of Bbsl result from biopsy
Acrodermatitis Chronica Atrophicans	Long-standing red or bluish-red lesions, usually on the extensor surfaces of extremities; initial doughy swelling; possible skin induration and fibroid nodules over bony prominences		Positive PCR/Culture of Bbsl result from biopsy
LB Ocular Manifestations	Conjunctivitis, uveitis, papillitis, episcleritis, or keratitis		•Positive PCR/Culture of Bbsl result from ocular fluid
Lyme carditis	Acute onset of high degree atrioventricular conduction disturbances, rhythm disturbances, myocarditis, or pericarditis		
Lyme arthritis	Marked swelling in one or few large joints, most often the knee		•Positive PCR/Culture of Bbsl result from synovial fluid or tissue
Lyme neuroborreliosis	Meningo-radiculitis (Bannwarth syndrome), facial palsy, meningitis, encephalomyelitis, or cerebral vasculitis		•Intrathecal IgM and/or IgG antibodies; •Positive intrathecal anti-Borrelia antibody index (CSF vs Serum) reflecting intrathecal antibody production; •Positive PCR/Culture of Bbsl result from cerebrospinal fluid

•EM case can be diagnosed on the basis of clinical symptoms alone. Case definitions for disseminated disease require laboratory confirmation.

•Results not presented here.

PROJECTED ANNUAL INCIDENCE CALCULATION METHODS

- **Incidence denominator** for each site based on number of patients in their practice

$$Incidence = \frac{LB\ Cases\ per\ year}{Population\ Denominator\ from\ Practice}$$

- **Incidence numerator:**
  - Sites had a partial year of surveillance (start date ranged from April to July 2021) and the timing of the Lyme season varied by location
  - To account for this, each site reported historical LB case counts from 2 prior years by month to allow assessment of expected proportion of LB cases that would have normally occurred during the specific surveillance period for each site

- Screening Log data captured any unenrolled LB cases (including final clinical diagnosis)

- **Laboratory confirmation:**
  - The proportion laboratory confirmed was calculated from LB cases with 2 available study serology specimens (ie, from both Visit 1 and Visit 2)
  - Skin biopsy results are not yet available, which will likely increase the laboratory confirmations

RESULTS

- Between April 8 and December 31, 2021, there were 433 suspected LB cases, of which 351 (81%) were newly clinically-diagnosed LB cases (Figure 3).

- Among the LB cases (enrolled and unenrolled), 56.7% were female, and 72.6% were between the ages of 40 and 74 years. Eight pediatric cases were identified (one enrolled, seven unenrolled).

Figure 3. Flow of suspected LB cases

Total Screened: 433 Suspected LB Cases → Clinically-diagnosed LB 351 → Enrolled LB 269; Unenrolled LB 82
→ Not LB 82 → Enrolled Not LB 48; Unenrolled Not LB 226

- The overall projected incidence of LB (enrolled and unenrolled) was 657.2 per 100,000 per year, lower than in either of the previous years, varying from 188.8 in Poland to 3024.5 in Slovakia (Table 2, Figure 4).

- Slovakia reported a markedly different disease presentation to the other countries, with higher incidence in 2021 compared with previous years, and 71% of LB cases diagnosed as Lyme arthritis (Figures 4&5).

- Erythema migrans made up >95% of all cases reported by both Sweden and Slovenia (Figure 5).

- 61.3% of enrolled clinically diagnosed LB cases with available serology results at the time of analysis were lab-confirmed. There was notable variation between countries (20.0% in Poland to 71.0% in Sweden) (Table 2).

Table 2. Adjusted Incidence Rate of Clinically Diagnosed Lyme Borreliosis Through December 31, 2021

Countries	Sites	Practice Panel Size	Incidence per 100,000 in 2019 [a]	Incidence per 100,000 in 2020 [a]	All Study 2021 Lyme Disease Events [b]	Projected Annual LD Case Counts (2021) [c]	Projected Incidence per 100,000 in 2021 [e]	Percentage of LD Diagnoses Lab-Confirmed [d]	Projected Incidence of Lab-Confirmed LD per 100,000 in 2021 [f]
All Countries	All	65452	1088	1089	351	435.54	657.2	61.3	402.8
Czech Rep.	All CZ	9484	1233	1002	33	35.71	376.5	51.9	195.2
	1	4032	2183	1662	15	17.71	439.2	50.0	219.6
	2	1309	611.2	611.2	4	4.00	305.6	25.0	76.4
	3	4143	482.7	482.7	14	14.00	337.9	61.5	208.0
Germany	All DE	22590	629.3	527.8	44	51.75	229.1	66.7	152.7
	4	3549	140.9	169.1	4	6.34	235.0	50.0	117.5
	5	4687	735.6	853.1	11	12.11	258.3	75.0	193.7
	6	8168	621.4	354.5	15	16.38	195.9	87.5	171.4
	7	3887	1595	797.6	5	5.47	140.8	60.0	84.5
	8	2099	806.9	1006.5	9	9.43	449.5	40.0	179.8
Poland	9	5530	688.4	760.9	8	10.42	188.8	20.0	37.8
Slovakia	All SK	4032	1339	1314	97	121.95	3024	57.8	1747
	10	1974	2077	1771	70	84.71	4291	57.1	2452
	11	3059	631.7	874.6	27	37.24	1809	59.3	1072
Sweden	12	11056	2433	2066	148	170.24	1558	71.0	1106
Slovenia	13	13771	606.7	915.0	21	44.64	324.2	66.7	216.1

[a] Sum of Number of new LD diagnoses in corresponding year (Practice Panel), historical self-reported counts
[b] All Study 2021 Lyme Disease Events / Average percentage of annual LD cases (2019 and 2020) from that time period
[c] Projected Annual LD Case Counts (2021) / Practice Panel Size.
[d] Percentage of Laboratory Confirmed LD Diagnoses = Number of subjects with at least one positive result out of 2 available study specimens / Number of subjects with 2 study specimens with available.
[e] Projected Incidence per 100,000 in 2021 =
[f] Projected Incidence of LD Diagnoses Laboratory Confirmed.

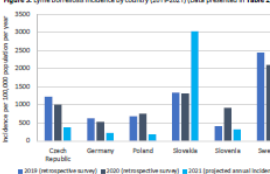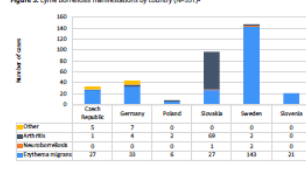**Figure 4.** Lyme borreliosis incidence by country (2019-2021) (Data presented in Table 2)

■ 2019 (retrospective survey) ■ 2020 (retrospective survey) ■ 2021 (projected annual incidence)

Figure 5. Lyme borreliosis manifestations by country (N=351)•

	Czech Republic	Germany	Poland	Slovakia	Sweden	Slovenia
Other	5	7	0	0	0	0
Arthritis	1	4	2	69	2	0
Neuroborreliosis	0	0	0	1	3	0
Erythema migrans	27	33	6	27	143	21

• Acrodermatitis chronica atrophicans, borrelial lymphocytoma and ocular manifestations were not reported. Cases with more than one manifestation are counted toward only one manifestation. The manifestation was unknown for one unenrolled case.

DISCUSSION & CONCLUSIONS

- The overall projected incidence of LB was 657.2 per 100,000 in 2021. There was substantial variation across participating countries.

- Many investigators noted that less LB was seen in 2021 than previous years possibly due to a cool spring and dry summer

- Given 73% (257/351) of LB was erythema migrans of which only ~50% would seroconvert4, about 60% of events were expected to seroconvert based on known test performance

- specifications. 61.3% of cases with serology results to date were lab-confirmed. Laboratory confirmation rates will likely be higher when skin biopsy culture & PCR are included

- Multiple factors may play a role in the higher proportion of Lyme arthritis cases observed in Slovakia, such as COVID-19-related delayed healthcare seeking behavior, and possibly some over diagnosis.

1. Lindgren E & Jaenson TGT. WHO, Regional Office for Europe 2006.
2. Sykes RA & Makiello P. J Public Health (Oxf). 2017;39(1):74-81.
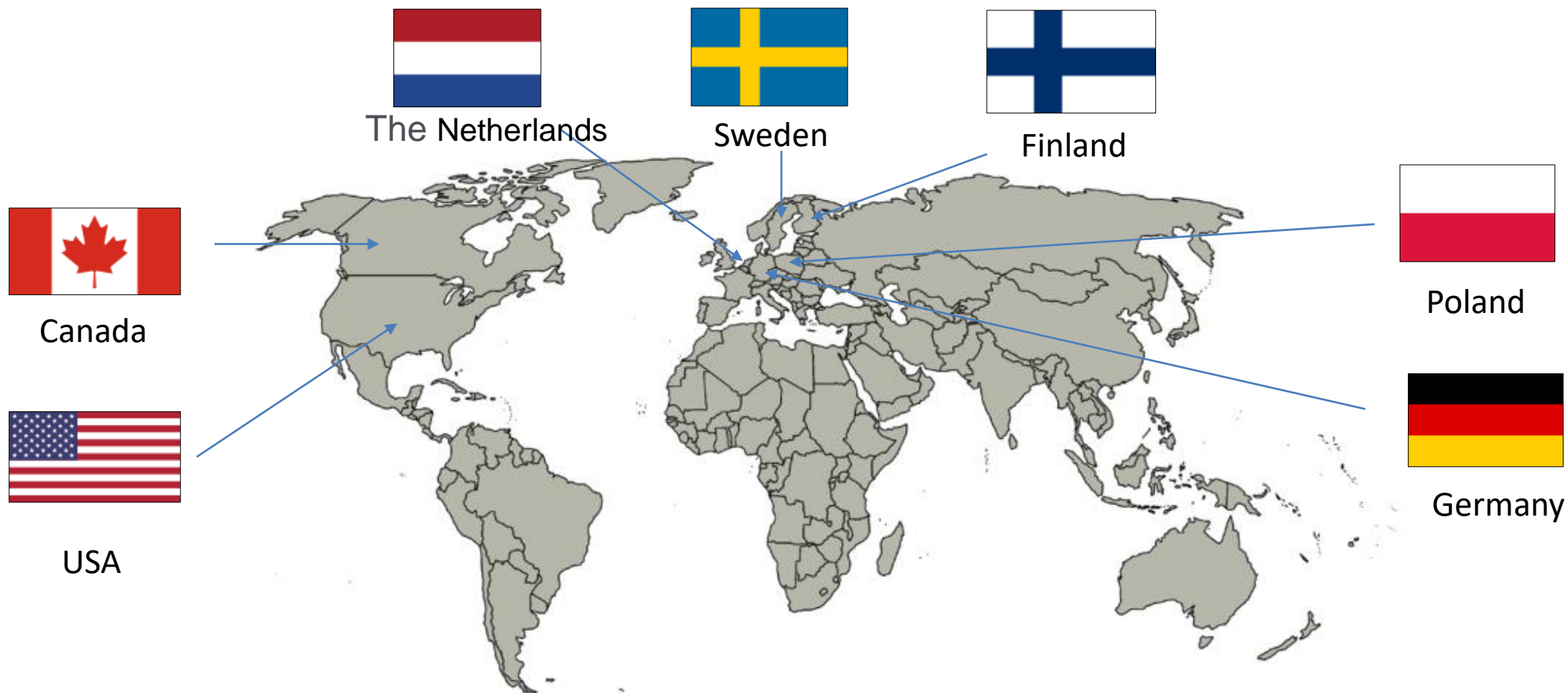3. Stanek G, et al. Clin Microbiol Infect. 2011;17(1):69-79.

VALOR

- Pfizer and Valneva collaborate on 6-Valent OspA-based VLA15 vaccine against Lyme Disease caused by *Borrelia burgdorferi* sensu lato
- VLA15 covers 6 serotypes – the most prevalent in North America and Europe
- VLA15 demonstrated strong immunogenicity and safety in preclinical and phase 1 and 2 studies

VALOR

VALOR

- Approximately 9,000 healthy participants
- ≥ 5 years of age
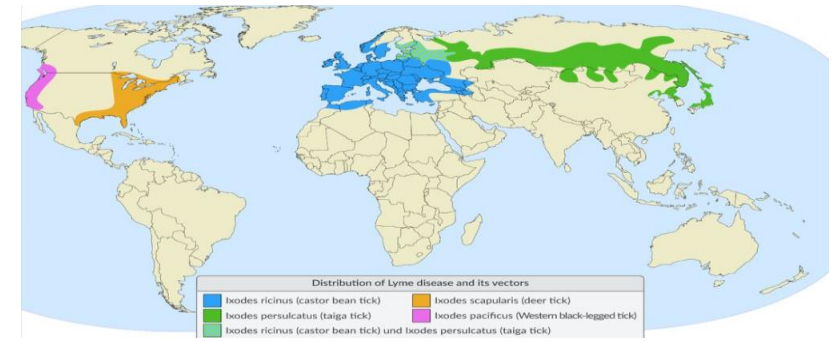- From areas with high levels of endemic Lyme disease
- VLA15 or placebo

Lyme disease - Challenges

- Limitations of current standards of care

- **Faster detection of infection means fewer health problems**

- EARLY diagnosis of Lyme disease allows for identification of infected individuals and treatment before the disease becomes severe

- Although the clinical condition may manifest itself within a few days of a tick bite, the standard two-step serological test sTTT does not meet the conditions for detecting the disease in the EARLY stage

- LIAISON® LymeDetect® combines the proven LIAISON® Borrelia IgG and IgM CLIA tests with the patented QuantiFERON® IGRA technology, **increasing the sensitivity of EARLY diagnosis from 48.5% to 73.5% compared to sTTT**

A new paradigm in EARLY diagnostics

- LIAISON® LymeDetect® measures both **B-cell humoral immunity and T-cell immunity**, enabling the successful diagnosis of Lyme disease within weeks of contact with an infected tick

- In contrast to manual procedures that are subject to the possibility of simple human error, LIAISON® LymeDetect® is a closed-loop system that provides **a clear and reliable diagnostic solution that optimizes workflow and improves results**

- **Innovative and intuitive**

- When three reagent kits are placed in the LIAISON® XL or LIAISON® XS instrument for **automated CLIA testing**, the results are combined into a single quantitative test

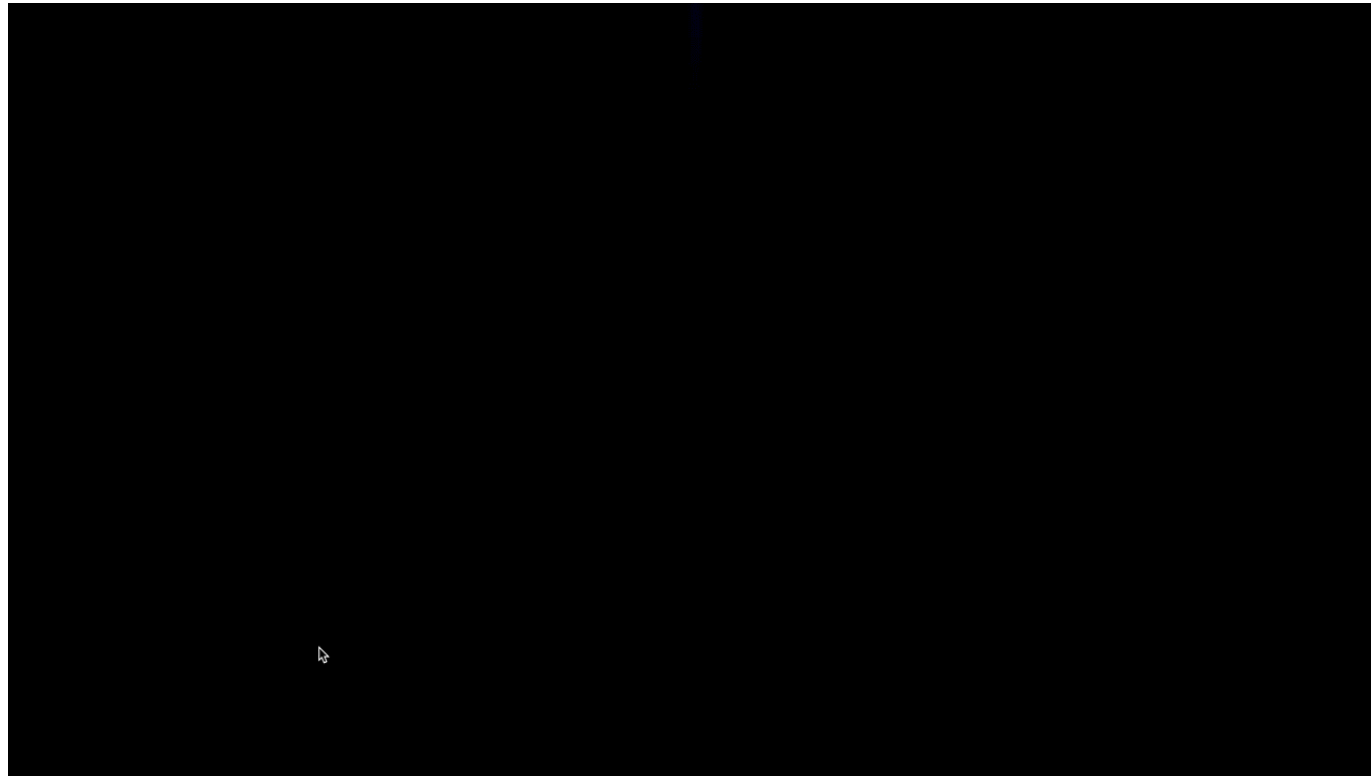- **Diagnosis available within 24 hours**

LIAISON® LymeDetect®

Nowy paradygmat WCZESNEGO
wykrywania boreliozy z Lyme

COVID-19 ...

Thank you for your attention

Justyna Adamczuk

Karol Borawski

Piotr Czupryna

Justyna Dunaj-Małyszko

Sambor Grygorczuk

Maciej Kondrusik

Ewelina Kruszewska

Anna Moniuszko-Malinowska

Sławomir Pancewicz

Joanna Zajkowska