How to protect individuals with high genetic risks from acquiring severe SARS-CoV2 infections?

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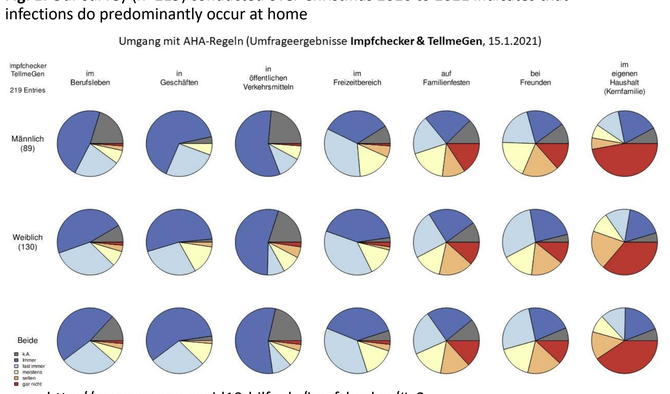
Abstract

Ongoing Corona studies have been initiated by the IndyMed-Consortium from beginning in March 2020: With the event of the SARS-CoV2 pandemic in March 2020, it became evident that people at elderly homes will run the highest risk to suffer from Covid-19 disease. In particular, in the early days the usage of non-pharmaceutical-interventions (NPI) has been the measure of choice. Initially, most of the deaths due to corona infections occurred predominantly in the population above 65-year-old, see Table 1 as well http://www.corona-covid19-hilfe.de/bundestag/index.php?covstatistik, primarily in individuals with high body mass index with manifested comorbidities such as diabetes mellitus or hypertension. Note, the analysis of corona infection and death rates broken down to cohorts of 10 year-segments of age indicates that less than 20% of elderly individuals at ages from 80 to 89 died from corona in 2020 and 2021 with a limited 2-fold effect most likely due to vaccinations in 2021 (Table 1). As outlined below, our research strategy consists of the understanding that Corona is an infection, but Covid-19 is a polygenic disease with the potential to be predictive.

Introduction

From the beginning of the SARS-CoV2 pandemic in March 2020, our research initiative (Institute of Immunology, University Medicine Rostock) claimed that Covid-19 is primarily a disease of the elderly (press release March 12, 2020). We consider Covid-19 to be a polygenic disease due to an interplay between individual host genome, immune system and age plus/minus comorbidities (Fig. 2). Our integrative research approach is outlined in Fig. 3 as presented to the Parliamentary Subcommittee Covid-19-Pandemic of the Bundestag on May 6th, 2021 (Google: Bundestag Hans-Juergen Thiesen). Note, commonly a significant number of individuals (n=26954 in 2020) die yearly at ages of 40 to 60 years (Fig. 6). Furthermore, the age dependent impact of SARS-CoV2 vaccinations in 2021 can nicely be compared with RKI data of unvaccinated in 2020 (Table 1) . Altered pathogenicity of Delta and Omicron become visible by comparing percentage of age dependent weekly Covid-19 death rates in December 2021 with weekly death rates in 2022. Note, SARS-CoV2 infections mainly occur in family settings at home: the final result of our survey (n=219) conducted over Christmas 2020 (Fig.1).

Fig. 1. Our survey (n=219) conducted over Christmas 2020 to 2021 indicates that infections do predominantly occur at home



see: http://www.corona-covid19-hilfe.de/impfchecker/#a3

Fig. 2. Integrative Computational Analysis of Features suspected to be involved in COVID-19 Disease

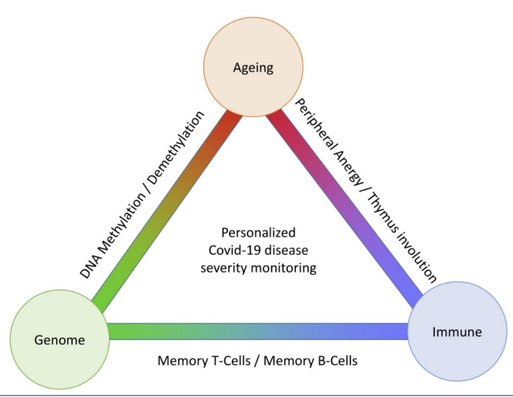


Fig. 3. Clinical studies from corona serology to host-genome analysis (plus vaccination studies conducted)

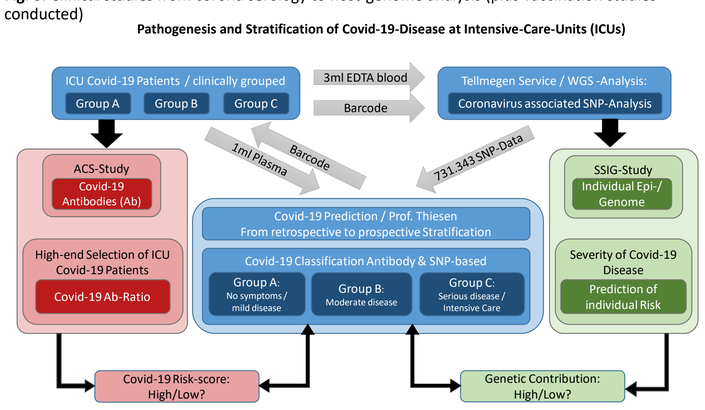


Fig. 4. General computational design how to compute polygenic traits

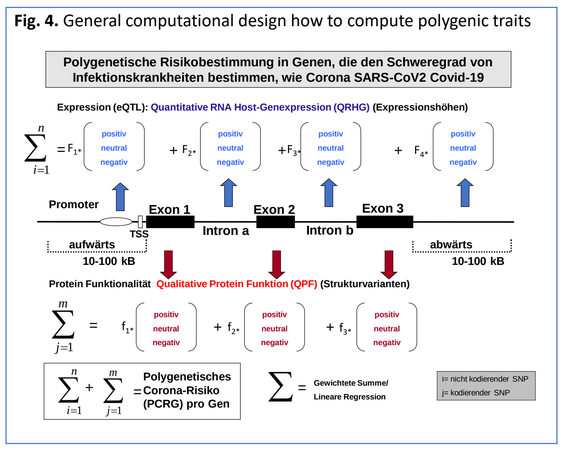


Fig. 5. Distribution of Corona Variants in Germany 2020 - 2022

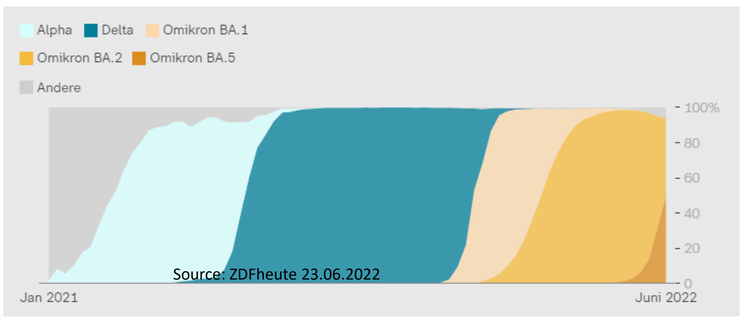
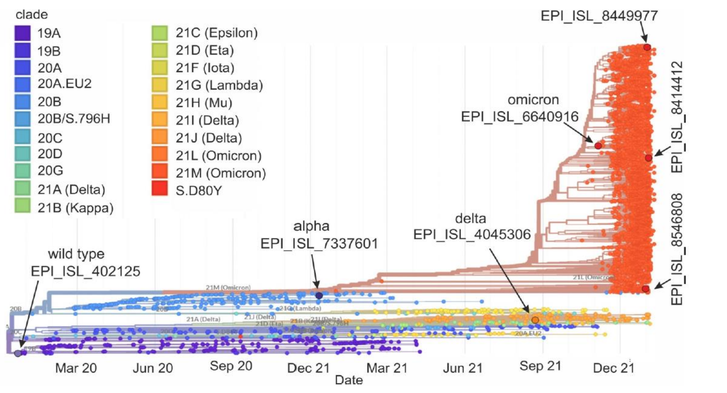


Fig S1. Phylogeny tree of SARS-CoV2 strains. Clades are color coded. Locations of SARS-CoV2 wt strain (EPI-ISL_402125) from Wuhan (GenBank: MN908947.3; spike protein UniProt P0DTC2), SARS-CoV2 α strain from South Africa (EPI_ISL_7337601), SARS-CoV2 δ strain from Germany (EPI_ISL_4045306), SARS-CoV2 o strain from Botswana (EPI_ISL_6640916), SARS-CoV2 o strain from Israel (EPI_ISL_8546808), SARS-CoV-2 o strain from Germany (EPI_ISL_8414412), and SARS-CoV2 o strain from Singapore (EPI_ISL_8449977) are shown Obtained from:
https://nextstrain.org/groups/neherlab/ncov/21K.Omicron?r=location



Tab. 1. Comparative Analysis of COVID-19 Death Rates broken down to Age and SARS-CoV2 Variance

Covid-19 Deaths												
Year	Age in years											
	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	90+	Total	
2020	12	6	60	97	276	1.154	3.298	8.500	20.470	10.261	44.134	Wuhan
2021	45	54	116	361	902	3.331	7.954	15.322	29.558	13.018	70.661	Alpha, Delta
2022 *	39	36	45	104	246	884	2.222	4.328	9.782	4.958	22.644	Omikron BA1, BA2

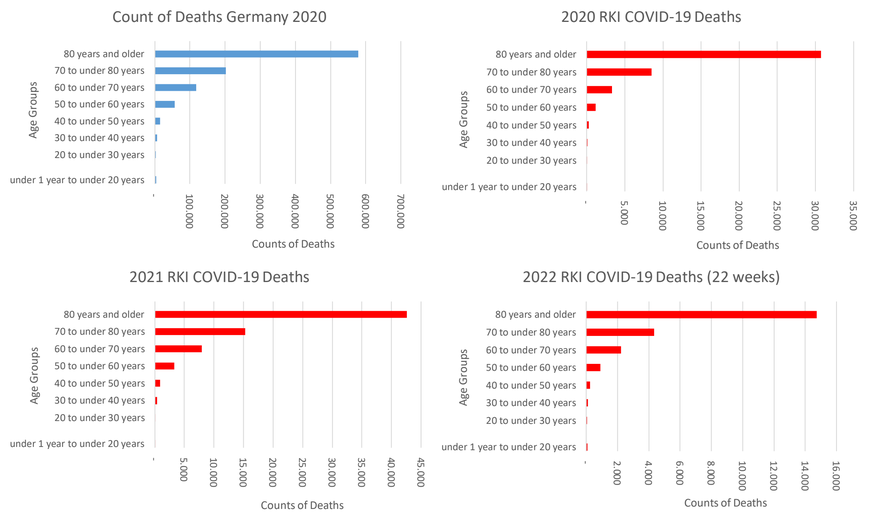
Covid-19 Infections												
Year	Age in years											
	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	90+	Total	
2020	76.486	162.212	287.630	267.472	255.393	300.569	164.102	102.055	120.536	45.283	1.781.738	Wuhan
2021	573.790	791.478	769.531	881.587	784.577	754.950	428.282	218.856	183.203	52.777	5.439.031	Alpha, Delta
2022 *	2.102.711	2.878.228	2.932.347	3.338.217	2.819.827	2.648.761	1.393.571	590.192	422.933	114.337	19.241.124	Omikron BA1, BA2

Covid-19 Death Rates												
Year	Age in years											
	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	90+	Total	
2020	0,02%	0,00%	0,02%	0,04%	0,11%	0,38%	2,01%	8,33%	16,98%	22,66%	2,48%	Wuhan
2021	0,01%	0,01%	0,02%	0,04%	0,11%	0,44%	1,86%	7,00%	16,13%	24,67%	1,30%	Alpha, Delta
2022 *	0,00%	0,00%	0,00%	0,00%	0,01%	0,03%	0,16%	0,73%	2,31%	4,34%	0,12%	Omikron BA1, BA2

* 22 weeks

Please, note, the analysis of corona infection and death rates broken down to cohorts of 10 year-segments of age indicate that less than 20% of elderly individuals died at ages from 80 to 89 from corona in 2020 to 2022. Our studies indicate that the percentage of Covid-19 deaths only show a 2-fold difference in the age groups between 2020 (nonvaccinated) and 2021 (vaccinated individuals), but a 10-fold difference between Delta and Omicron

Fig 6. Age dependent Covid-19 Death Rates in Germany 2020 till 2022 compared with overall death rates (here in 2020)



Material and Methods:

From March 2020, our Corona research objectives have been focused on three fundamental assumptions that are summarized in a triangle cartoon (Fig. 2) with focus on the host genome, the immune system and the presence of comorbidities in respect to age. As such, differences in death rates within age groups are most likely related to the presence of individual genetic single nucleotide (SNP) patterns in concert with individual immune status and the presence of comorbidities. Concepts of current pilot studies are outlined in Fig. 3: Most importantly, precise documentation of phenotypic Covid-19 symptoms turns out to be of unprecedented importance for comparing individual genomes of Covid-19 patients in a meaningful manner on the gene-based SNP level. Knowledge of BMI as well as stage and gradings of comorbidities are essential to separate Covid-19 host genomes with highly related from quite distinct Covid-19 phenotypes. Note our bioinformatic predictions in Fig. 7, Fig. 8., Fig. 9, and Fig. 10.

Objectives: Our comprehensive IndyMed concept regarding participation of ICU patients and patients that suffer from Long-Covid or Post-Vac symptoms.

I. DIVI medical doctors at ICUs in charge of treating Covid-19 patients are encouraged to join our IndyMed initiative as well as clinicians treating individuals with Long-Covid and with Post-Vac symptoms. Participants will be asked via an online survey for individual personal reports of symptoms as done in Fig. 1.

II. Based on the survey in concert with clinical documentation, blood samples are considered to firstly undergo antibody determination of Spike- and N-Capid-antibody titres, followed by SNP analysis to be conducted either by Tellmegen (Valencia in Spain) or by academic partners at Helmholtz Munich. We schedule to investigate samples of about 1000-2000 individuals in total. Comparable data sets have been analyzed in ongoing pilot experiments (Fig. 9 and Fig.10).

III. The most informative Covid-19 cases are considered to directly undergo whole genome analysis (Fig. 3). The others will be selected regarding whole genome sequence (WGS) analysis from about 1000-2000 Covid-19 patients based on medical reports and initial SNP typing results. About 100 to 200 whole genome sequencing samples are planned to be conducted in total.

IV. Based on Glocker et al., 2022, all 1000-2000 patients might as well be asked for consent to be HLA-typed to investigate whether specific MHC class I or MHC class II variants do play a role in disease susceptibility or disease severity, see computational analysis in Table S3.

V. Sera collected in 2021 and 2022 of SARS-CoV2 infected, immunized and boostered individuals are available for comparative high-end epitope studies as initially conducted at the Institute of Immunology in April/May 2017. Boosterings based on SARS-CoV2 related antibody titres might become the practice of choice.

VI. Note, our ongoing genome-wide SNP studies (Fig. 7, Fig. 8, Fig. 9 and Fig. 10) demonstrate, Covid-19 is most likely a polygenic disease with manifold phenotypes. The challenge to meet will be to compare host genomes with each other that clinically share similar SARS-CoV2 symptoms and comorbidities.

Table S3: Comparative Analysis of HLA class I peptides from spike proteins from Omicron variants and strains. [a,b,c]

	HLA-A0101	HLA-A0201	HLA-A0301	HLA-A2402	HLA-B0702	HLA-B0801	HLA-B1503	HLA-B3501	HLA-B4001	HLA-B4402
Strong Binder										
EPI_ISL_402125	2	13	5	4	2	2	41	18	2	1
EPI_ISL_6640916	2	12	5	4	2	2	38	17	2	1
EPI_ISL_8414412	3	11	6	5	1	2	38	18	2	1
EPI_ISL_8449977	3	11	6	5	1	2	38	18	2	1
EPI_ISL_8546808	2	12	5	4	1	2	41	18	2	1
Medium Binder										
EPI_ISL_402125	4	25	18	10	10	15	94	34	5	4
EPI_ISL_6640916	4	27	18	11	7	15	100	35	4	3
EPI_ISL_8414412	3	26	18	9	8	16	102	33	4	3
EPI_ISL_8449977	3	26	18	9	8	16	101	33	4	3
EPI_ISL_8546808	3	24	18	9	9	15	96	33	5	4
Nonbinder										
EPI_ISL_402125	1259	1227	1242	1251	1253	1248	1130	1213	1258	1260
EPI_ISL_6640916	1256	1223	1239	1247	1253	1245	1124	1210	1256	1258
EPI_ISL_8414412	1253	1222	1235	1245	1250	1241	1119	1208	1253	1255
EPI_ISL_8449977	1253	1222	1235	1245	1250	1241	1120	1208	1253	1255
EPI_ISL_8546808	1255	1224	1237	1247	1250	1243	1123	1209	1253	1255

a) numbers of peptides with high, medium, or no binding affinity are listed as determined by the NetMHC 4.0 Server.
b) HLA-B1503 has the highest number of strong and/or medium binding peptides.
c) the lowest number of strong binding peptides is present in HLA-B4402.

As published February 2, 2022, in Medicina by Glocker et al., our abstract focuses on free energy calculations of SARS-CoV2 spike protein receptor binding motives (RBMs) from wild type and variants of concern (VOCs), with emphasis on SARS-CoV2 Omicron. Our computational analysis underlines the occurrence of positive selection processes that specify Omicron host adaption and bring changes on the molecular level into context with clinically relevant observations. Our free energy calculation studies regarding the interaction of Omicron ´s RBM with human angiotensin converting enzyme 2 (hACE2) indicate weaker binding to the receptor than Alpha´s or Delta´s RBMs, see Fig. 1. Upon weaker binding, fewer viruses are predicted to be generated in time per infected cell, resulting in a delayed induction of danger signals as a trade-off. Along with delayed immunogenicity and pathogenicity, more viruses may be produced in the upper respiratory tract, explaining enhanced transmissibility. The interdependence regarding the human leukocyte antigen types (HLA types) requires further investigation, see Table S 3.In case of Omicron, more SARS-CoV2 viruses are assumed to be required to initiate inflammatory immune responses. Note, pre-existing partial immunity through previous infections and/or vaccinations mostly guard the lower respiratory tract from Delta infections. In case of Omicron, overall disease severity was claimed to become reduced. Recent RKI data in Table 1: lethality of Omicron is reduced by 10-fold.

Interestingly, our computational calculations of corona variants predicted, published in bioRxiv on December 15th, 2021, that omicron infections might lead to reduced covid-19 lethalities (https://doi.org/10.1101/2021.12.14.472585).

BioRxiv_Abstract (Glocker et al., December 15th, 2021: Our study focuses on free energy calculations of SARS-CoV2 spike protein receptor binding motives (RBMs) from wild type and variants of concern with particular emphasis on currently emerging SARS-CoV2 omicron variants of concern (VOC). Our computational free energy analysis underlines the occurrence of positive selection processes that specify omicron host adaption and bring changes on the molecular level into context with clinically relevant observations. Our free energy calculations studies regarding the interaction of omicron's RBM with human ACE2 shows weaker binding to ACE2 than alpha's, delta's, or wild type's RBM, see Figure S1. Thus, less virus is predicted to be generated in time per infected cell. Our mutant analyses predict with focus on omicron variants a reduced spike protein binding to ACE2 receptor protein possibly enhancing viral fitness / transmissibility and resulting in a delayed induction of danger signals as tradeoff. Finally, more virus is produced but less per cell accompanied with delayed Covid-19 immunogenicity and pathogenicity.

Interestingly, computational calculations predicted that omicron infections should lead to reduced lethality. As demonstrated in Table 1, the lethality rates dropped from 2,48 % in 2020 to 1,3 % in 2021 and to 0,12% in 2022. Lethality rates in 2022 collected by the Robert-Koch-Institute (RKI) revealed an about ten-fold drop in lethality rates (Table 1). Our studies indicate that the percentage of deaths only show a twofold difference in the age groups between 2020 (nonvaccinated) and 2021 (vaccinated individuals), but a tenfold difference is visible between death rates between Delta and Omicron (Table 1).

As reported by comparative analysis of experimental data of W. Barclay's research team in bioRxiv https://doi.org/10.1101/2021.12.31.474653 Omicron appears to be inherently more transmissible than previous variants, with a shorter serial interval than Delta, but is also associated with less severe disease and shows attenuated fusogenicity and a preference for cell entry via the endosomal route independent of the presence of TMPRSS2.

Conclusion: In particular, the project's research program outlines the following steps to meet the challenge of forthcoming SARS-CoV2 infections: The health authorities and decision maker might recapitulate their Corona policies from the beginning of the SARS-CoV2 pandemic in March 2020. Study the official age-dependent death rates from 1 to 49 years old in Table 1 with the focus on Covid-19 deaths. 451 Covid-19 deaths are reported in 2020, 1478 deaths in 2022 and 470 deaths within the first 22 weeks in 2022. Note, according to Statista 2022, the yearly age-dependent deaths of individuals from 1 year to under 50 years of age was in 2020 n=26954 deaths vs. n= 451 Corona deaths in Germany.

We as IndyMed consortium propagate to encourage the scientific community and the society in general including the individuals that suffer from comorbidities to assess your own covid-19 risk (one of the issues in P4 Medicine, the participatory component). In case a personal Covid-19 risk score can be validated, policy maker might focus on protecting individuals at high risk without harming public life or interfering with socio-economic needs of the whole society.

Fig. 7. SNP analysis of SNP patterns upstream designating comorbidity genes using completely sequenced genomes.

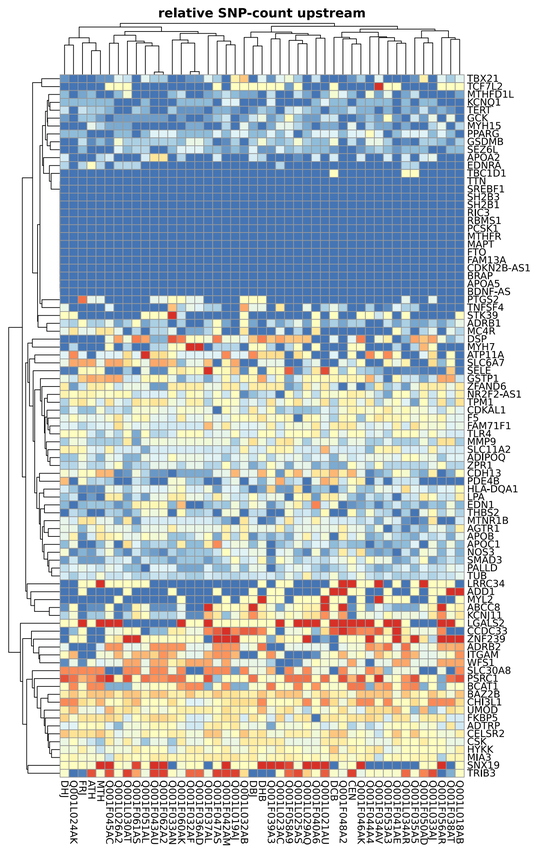


Fig. 8. SNP analysis of SNP patterns of exonic regions designating comorbidity genes based on completely sequenced genomes.

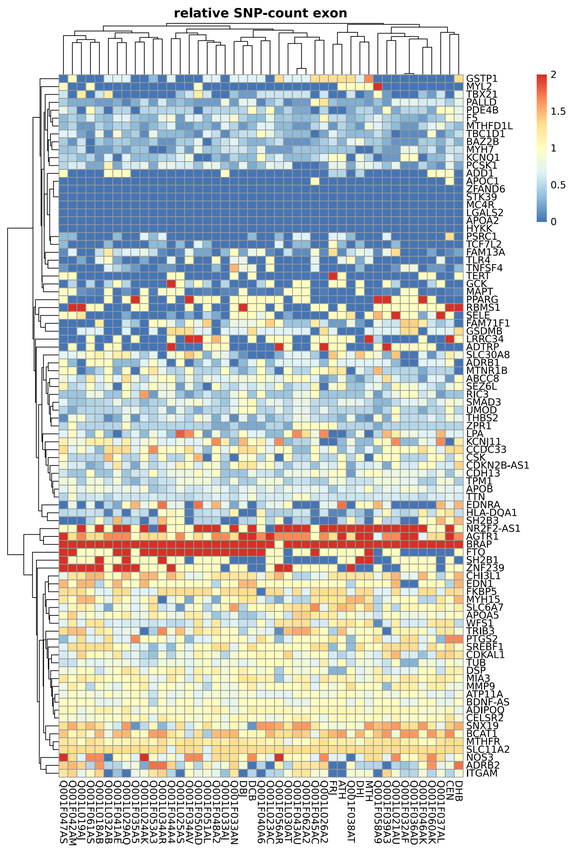


Fig. 9. Covid-19 genes selected from COVID19-HGI & Ellinghaus et al., 2020

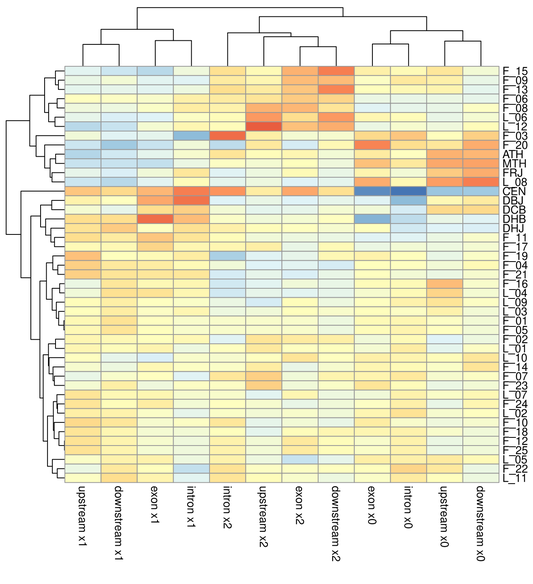
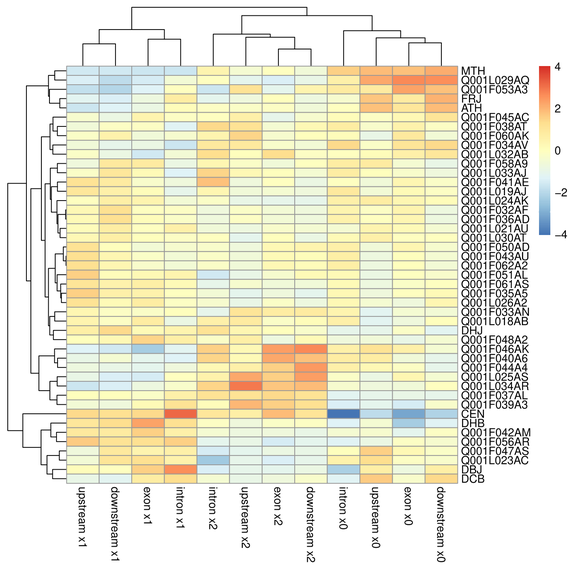


Fig. 10. Longevity-related gene-set with focus on CEN being 109 years of age



Results: The challenge of our IndyMed initiative is to determine criteria that enable health professionals to predict whether an individual will experience asymptomatic/mild or even severe life threatening Covid-19 symptoms, see Fig. 3.

Serology: Our vaccination studies indicate that about 1 to 2 in hundred individuals do not efficiently respond to current vaccination protocols. Furthermore, nonvaccinated individuals infected with Omicron do not display strong immune responses in comparison to individuals infected with SARS-CoV2 variants in 2021. Individual healthcare workers have been identified by us to have antibody responses against Corona proteins without having experienced SARS-CoV2 symptoms. One might hypothesize that low responders at young age might become Covid-19 patients at older age, in case these individuals will suffer from additional comorbidities.

Two general questions might be answered in our vaccination / SARS-CoV2 serological studies, whether low responders to vaccines and/or individuals with side effects to COVID-19 vaccinations (Post-Vac syndromes: https://doi.org/10.1186/s12985-022-01831-0) are at risk to get COVID-19 in case of infections. Forthcoming boostering should be based on timely antibody titre measures. Efficient Omicron vaccines are not yet available.

Host-Genome Analysis: Covid-19 patients initially treated at ICUs in Bad-Lippspringe (encoded in Figs. 7 to 10 with L) and in Frankfurt (encoded in Figs. 7 to 10 with F) gave their consent to get their genomes completely sequenced. Our ongoing computational analysis accordingly to Fig. 4 underscore the common challenge: clinical information including BMI, age and gender are essential to subgroup Covid-19 patients phenotypically prior to computational efforts to establish a personalized polygenic risk score suitable to stratify subgroups of vulnerable individuals at risk for getting Covid-19 disease. In Fig. 7 and Fig. 8 gene segments are selected that encompass genes associated with comorbidities in Covid-19 disease. Gene sets in Fig. 9 have already defined by Ellinghaus et al., 2020 and the COVID19-Host-Genome initiative to be related with Covid 19 disease. Genes related with longevity have been computationally analyzed in Fig. 10.

Discussion: The overall objective of our current IndyMed-Initiative entitled "Covid-P4: Assessment of personalized genome-based Covid-19 risk scores predicting the severity of Covid-19 disease" asked the scientific community for concerted action to support the public currently struck by the corona pandemics and associated lockdown measures since March 2020.

- Our scientific objectives in particular focus on stratifying the most highly vulnerables by means listed in Fig. 1, Fig. 2, Fig. 3 and Fig. 4, by making use of serology, medical observations and of whole genome analysis.

From the beginning of the Corona pandemic, we focused on determining differences in death rates within age groups in relation to individual immune status, comorbidity status and age, see Fig. 2. We are convinced that comprehensive Covid-19 risk data analyses should consist of individual corona surveys regarding medical history and corona symptoms , followed by the assessment of individual antibody titres against SARS-CoV2 Spike- and N-Capsid proteins plus adapted SNP-based risk assessments of comorbidity genes associated with Covid-19 disease to identify individuals that are most vulnerable. In ongoing studies, we favour the comparative SNP host-genome-analyses using completely sequenced genomes derived from Covid-19 at ICUs in respect to elderly as outliers that hardly showed any symptoms of infection while having stayed in elderly homes in 2020 plus having been in closed contact with healthy elderly that died from Covid-19 infection. Herein, CEN is taken as a substitute of being a healthy elderly outlier. CEN (109 years old) has never experienced any disease besides surgery for gallbladder stones.

Our genome data will be made available to the scientific community according to the guidelines of DECOI following as well as the RDA COVID-19 Recommendations. Our data repositories documentation offer the possibility of subsequent reuse of these data sets by other researchers as well. According to our own data analysis we encourage individuals being afraid to belong to the group of highly vulnerables to ask for Direct to Consumer (DTC) genetic testing to assess their individual genetic risk in combination with BMI, age, medical history, lifestyle in concert with timely determined corona antibody titres.

Autumn 2022, the best individual protection besides NPI and reduced contacts will be in case of SARS-CoV2 symptoms personal testing of Corona virus positivity at home (best in the morning), timely assessment of antibody levels against SARS-CoV2 spike & N-capsid proteins in respect to age, BMI, comorbidity plus DTC SNP testing and clear instructions for self-quarantine.