LEGISLATIVE ASSEMBLY
FOR THE AUSTRALIAN CAPITAL TERRITORY

STANDING COMMITTEE ON HEALTH AND COMMUNITY WELLBEING
Mr Johnathan Davis MLA (Chair), Mr James Milligan MLA (Deputy Chair),
Mr Michael Pettersson MLA

Submission Cover Sheet

Inquiry into Public Health Amendment Bill 2021 (No 2)

Submission Number: 0974

Date Authorised for Publication: 18 January 2022

Mark Searle
[redacted]

MR JOHNATHAN DAVIS MLA (CHAIR)
THE STANDING COMMITTEE ON HEALTH AND COMMUNITY WELLBEING
ACT LEGISLATIVE ASSEMBLY
GPO BOX 1020
CANBERRA ACT 2601

Dear Johnathan,

re: Call for Submissions on Public Health Amendment Bill 2021 (No 2)

I was born here in Canberra and have lived here for the majority of my life. My children were also born here and I have been raising them for many years in this wonderful city.

I have some serious concerns regarding my children, their future and the future of all residents of the ACT if the ACT Government approves the amendments to the Public Health Act.

Firstly, why is the Bill being considered when the vaccines are in clinical trials until 2023? Clinical trial end dates can be found at the following links:

AstraZeneca concludes February 2023:
https://clinicaltrials.gov/ct2/show/NCT04516746

Pfizer trials conclude May 2023:
https://clinicaltrials.gov/ct2/show/NCT04368728

Moderna concludes October 2022:
https://clinicaltrials.gov/ct2/show/NCT04470427

My concern is that the Bill pre-empts the findings of the clinical trials. It subjects Australian citizens to the clinical trials in contravention of the Nuremberg Code (1947). An extract of the code with regards to permissible medical experiments is at Attachment A.

The Nuremberg Code (1947) and permissible medical experiments:

1. The voluntary consent of the human subject is ***absolutely essential****. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.*

I request that all members of the Standing Committee on Health and Community Wellbeing reads the document at Attachment B titled:

Cumulative Analysis of Post Authorisation Adverse Event Reports of PF-07302048 (BNT162B2) Received through 28-FEB-2021

This document was obtained via a Freedom of Information Act (FOIA) request which was filed by a United States government accountability group called Public Health and Medical Professionals for Transparency.

Justice Department lawyers representing the US FDA requested 75 years to process the FOIA and agreed to release 500 pages of clinical trial data per month. The document at Attachment B is the first document released under the FOIA request and it paints a grim picture; in the first 90 days of the vaccine's roll out under the FDA's emergency use authorisation (1 December 2020 – 28 February 2021) there were tens of thousands of reported adverse reactions, including over 1200 deaths.

Combined with the real-time statistics coming out of the USA, UK, Europe and Australia, the numbers of Covid-19 vaccination adverse reactions and deaths are deeply concerning:

US VAERS (Vaccine Adverse Event Reporting System) as at 24 December 2021:
- 1,859,633 adverse reactions, 30,250 deaths
- https://openvaers.com/

UK Yellow Card as at 20 December 2021:
- 1,354,228 adverse reactions, 1,889 deaths
- https://yellowcard.ukcolumn.org/yellow-card-reports

EU Eudra Vigilance as at 18 December 2021:
- 3,120,439 adverse reactions, 34,337 deaths
- https://vaccineimpact.com/2021/34337-deaths-3120439-injuries-following-covid-shots-in-european-database-as-uk-public-data-show-35-deaths-213-hospitalizations-among-booster-triple-vaccinated/

AU Therapeutic Good Association DAEN as at 23 December 2021:
- 94,047 adverse reactions, 719 deaths
- https://www.tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-23-12-2021

If you factor in that only 1% of adverse reactions are reported as per the research grant given on "Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP:VAERS)" compiled by Harvard Pilgrim Health Care Inc (Attachment C, page 6, results), the number of adverse reactions and death could be akin to genocide.

I would also draw your attention to the thousands of people on this website who have shared their stories of Covid vaccine injuries from around the world:

https://linktr.ee/jabinjuriesglobal

This Bill, which seeks to give the ACT Government power to require people to have a COVID-19 vaccinations for: "their work, an activity, attending a place; working in particular places", as well as giving conditional powers for the Chief Health Officer to require a person to take a test, to isolate, and provide information (in an effort to suppress the spread of covid), does not out-weigh the risk of physical and physiological harm, being inflicted by these experimental injections. A risk that has been acknowledged by the Australian Government Department of Health who have added a new item to the Medicare Benefits Scheme (Attachment D):

From 1 January 2022, Medicare Benefits Schedule (MBS) item 63399 is being introduced for cardiac magnetic resonance imaging (MRI) to assist in diagnosing myocarditis that may occur after vaccination with the mRNA COVID-19 vaccines Comirnaty (Pfizer) and Spikevax (Moderna).

I believe this risk is further exacerbated by the experimental vaccines use of genetically modified organisms (GMOs) as per the Australian government's current policy on COVID-19 vaccines that states on Page 5 that:

'The OGTR will be required to approve and license any COVID-19 vaccines being administered in Australia that use GMOs. These include all the adenovirus vaccines and some of the mRNA vaccines'.

https://www.health.gov.au/sites/default/files/documents/2020/12/covid-19-vaccination-australian-covid-19-vaccination-policy.pdf

Some of the risks are set out in Attachment E, a US Supreme Court Opinion Piece that discusses the inability to patent human DNA but admits the eligibility to patent synthetically created DNA known as complementary DNA (cDNA). cDNA is introduced to cells via mRNA technology. The ACT Government cannot risk any of its tax-paying men and women being owned by the corporations that patent 'vaccine' technology. This is inherently wrong.

There is more than sufficient evidence to suggest that any law that requires a person to be vaccinated for Covid-19 would be enacted with the foreknowledge of a real and present danger to that individual and with the foreknowledge that it can cause harm to that individual. This implies a criminal act. If the Health Amendment Bill 2021 is passed and the men and women of Canberra are required to show vaccination status to enter work, places and do activities, the ACT Government will be in violation of the Nuremburg Code as we are subjected to force, fraud, deceit, duress, overreaching and other ulterior forms of constraint or coercion. From the onset of Covid, we have been told, relentlessly, by our government and media, that the vaccines are safe and effective. Two years down the track, the numbers and research are telling a very different story, to such a degree in fact, that all Covid-19 vaccinations programs should be halted immediately.

Let it be known that I DO NOT CONSENT to the Health Amendment Bill which is seeking to insert Part 6C and Part 7A to "Introduce and establish a regulatory framework for protecting the public from the public health risks of COVID-19 in circumstances where those risks may not give rise to a public health emergency".

Let it be known that I DO NOT CONSENT to the inclusion of new temporary powers which would give any man or woman the power to implement public health and social measures, including COVID-19 vaccination requirements for certain workers, and test, trace, isolate and quarantine measures to supress or prevent the spread of COVID-19 within the community.

The Covid-19 vaccination program is an experimental gene therapy which contains complimentary DNA, undisclosed nanotechnology, GMOs and the cells from monkeys and aborted babies. The Health Amendment Bill 2021 (2) is in direct violation of the Nuremburg Code and any man or woman who approves this Bill whilst holding title of office within the ACT Government, must be held accountable for all deaths and injuries inflicted by these injections.

I would urge you to govern yourself with honour and integrity and for the good of the people in the ACT.

Warm regards,

Mark Searle
13/01/2022

THE NUREMBERG CODE

Permissible Medical Experiments

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Of the ten principles which have been enumerated our judicial concern, of course, is with those requirements which are purely legal in nature — or which at least are so clearly related to matters legal that they assist us in determining criminal culpability and punishment. To go beyond that point would lead us into a field that would be beyond our sphere of competence. However, the point need not be labored. We find from the evidence that in the medical experiments which have been proved, these ten principles were much more frequently honored in their breach than in their observance. Many of the concentration camp inmates who were the victims of these atrocities were citizens of countries other than the German Reich. They were non-German nationals, including Jews and "asocial persons", both prisoners of war and civilians, who had been imprisoned and forced to submit to these tortures and barbarities without so much as a semblance of trial. In every single instance appearing in the record, subjects were used who did not consent to the experiments; indeed, as to some of the experiments, it is not even contended by the defendants that the subjects occupied the status of volunteers. In no case was the experimental subject at liberty of his own free choice to withdraw from any experiment. In many cases experiments were performed by unqualified persons; were conducted at random for no adequate scientific reason, and under revolting physical conditions. All of the experiments were conducted with unnecessary suffering and injury and but very little, if any, precautions were taken to protect or safeguard the human subjects from the possibilities of injury, disability, or death. In every one of the experiments the subjects experienced extreme pain or torture, and in most of them they suffered permanent injury, mutilation, or death, either as a direct result of the experiments or because of lack of adequate follow-up care.

Obviously all of these experiments involving brutalities, tortures, disabling injury, and death were performed in complete disregard of international conventions, the laws and customs of war, the general principles of criminal law as derived from the criminal laws of all civilized nations, and Control Council Law No. 10. Manifestly human experiments under such conditions are contrary to "the principles of the law of nations as they result from the usages established among civilized peoples, from the laws of humanity, and from the dictates of public conscience."

Whether any of the defendants in the dock are guilty of these atrocities is, of course, another question Under the Anglo-Saxon system of jurisprudence every defendant in a criminal case is presumed to be innocent of an offense charged until the prosecution, by competent, credible proof, has shown his guilt to the exclusion of every reasonable doubt. And this presumption abides with the defendant through each stage of his trial until such degree of proof has been adduced. A "reasonable doubt" as the name implies is one conformable to reason — a doubt which a reasonable man would entertain. Stated differently, it is that state of a case which, after a full and complete comparison and consideration of all the evidence, would leave an unbiased,

unprejudiced, reflective person, charged with the responsibility for decision, in the state of mind that he could not say that he felt an abiding conviction amounting to a moral certainty of the truth of the charge.

If any of the defendants are to be found guilty under counts two or three of the indictment it must be because the evidence has shown beyond a reasonable doubt that such defendant, without regard to nationality or the capacity in which he acted, participated as a principal in, accessory to, ordered, abetted, took a consenting part in, or was connected with plans or enterprises involving the commission of at least some of the medical experiments and other atrocities which are the subject matter of these counts. Under no other circumstances may he be convicted.

Before examining the evidence to which we must look in order to determine individual culpability, a brief statement concerning some of the official agencies of the German Government and Nazi Party which will be referred to in this judgment seems desirable.

Source
THE NUREMBERG CODE [from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10.* Nuremberg, October 1946–April 1949. Washington, D.C.: U.S. G.P.O, 1949–1953.]

5.3.6 CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT REPORTS OF PF-07302048 (BNT162B2) RECEIVED THROUGH 28-FEB-2021

Report Prepared by:

Worldwide Safety

Pfizer

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LIST OF ABBREVIATIONS

Acronym	Term
AE	adverse event
AESI	adverse event of special interest
BC	Brighton Collaboration
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
DLP	data lock point
EUA	emergency use authorisation
HLGT	(MedDRA) High Group Level Term
HLT	(MedDRA) High Level Term
MAH	marketing authorisation holder
MedDRA	medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency
PCR	Polymerase Chain Reaction
PT	(MedDRA) Preferred Term
PVP	pharmacovigilance plan
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
RSI	reference safety information
TME	targeted medically event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	standardised MedDRA query
SOC	(MedDRA) System Organ Class
UK	United Kingdom
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VAERS	vaccine adverse event reporting system

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1. INTRODUCTION

Reference is made to the Request for Comments and Advice submitted 04 February 2021 regarding Pfizer/BioNTech's proposal for the clinical and post-authorization safety data package for the Biologics License Application (BLA) for our investigational COVID-19 Vaccine (BNT162b2). Further reference is made to the Agency's 09 March 2021 response to this request, and specifically, the following request from the Agency.

"Monthly safety reports primarily focus on events that occurred during the reporting interval and include information not relevant to a BLA submission such as line lists of adverse events by country. We are most interested in a cumulative analysis of post-authorization safety data to support your future BLA submission. Please submit an integrated analysis of your cumulative post-authorization safety data, including U.S. and foreign post-authorization experience, in your upcoming BLA submission. Please include a cumulative analysis of the Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in your Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). Please also include distribution data and an analysis of the most common adverse events. In addition, please submit your updated Pharmacovigilance Plan with your BLA submission."

This document provides an integrated analysis of the cumulative post-authorization safety data, including U.S. and foreign post-authorization adverse event reports received through 28 February 2021.

2. METHODOLOGY

Pfizer is responsible for the management post-authorization safety data on behalf of the MAH BioNTech according to the Pharmacovigilance Agreement in place. Data from BioNTech are included in the report when applicable.

Pfizer's safety database contains cases of AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these

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proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.

- An accumulation of adverse event reports (AERs) does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

- Among adverse event reports received into the Pfizer safety database during the cumulative period, only those having a complete workflow cycle in the safety database (meaning they progressed to Distribution or Closed workflow status) are included in the monthly SMSR. This approach prevents the inclusion of cases that are not fully processed hence not accurately reflecting final information. Due to the large numbers of spontaneous adverse event reports received for the product, the MAH has prioritised the processing of serious cases, in order to meet expedited regulatory reporting timelines and ensure these reports are available for signal detection and evaluation activity. The increased volume of reports has not impacted case processing for serious reports, and compliance metrics continue to be monitored weekly with prompt action taken as needed to maintain compliance with expedited reporting obligations. Non-serious cases are entered into the safety database no later than 4 calendar days from receipt. Entrance into the database includes the coding of all adverse events; this allow for a manual review of events being received but may not include immediate case processing to completion. Non-serious cases are processed as soon as possible and no later than 90 days from receipt. Pfizer has also taken a multiple actions to help alleviate the large increase of adverse event reports. This includes significant technology enhancements, and process and workflow solutions, as well as increasing the number of data entry and case processing colleagues. To date, Pfizer has onboarded approximately (b) (4) additional full-time employees (FTEs). More are joining each month with an expected total of more than (b) (4) additional resources by the end of June 2021.

3. RESULTS

3.1. Safety Database

3.1.1. General Overview

It is estimated that approximately (b) (4) doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 28 February 2021.

Cumulatively, through 28 February 2021, there was a total of 42,086 case reports (25,379 medically confirmed and 16,707 non-medically confirmed) containing 158,893 events. Most cases (34,762) were received from United States (13,739), United Kingdom (13,404) Italy (2,578), Germany (1913), France (1506), Portugal (866) and Spain (756); the remaining 7,324 were distributed among 56 other countries.

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Table 1 below presents the main characteristics of the overall cases.

Table 1. General Overview: Selected Characteristics of All Cases Received During the Reporting Interval

Characteristics		Relevant cases (N=42086)
Gender:	Female	29914
	Male	9182
	No Data	2990
Age range (years): 0.01 -107 years Mean = 50.9 years n = 34952	≤ 17 18-30 31-50 51-64 65-74 ≥ 75 Unknown	175[a] 4953 13886 7884 3098 5214 6876
Case outcome:	Recovered/Recovering	19582
	Recovered with sequelae	520
	Not recovered at the time of report	11361
	Fatal	1223
	Unknown	9400

a. in 46 cases reported age was <16-year-old and in 34 cases <12-year-old.

As shown in Figure 1, the System Organ Classes (SOCs) that contained the greatest number (≥2%) of events, in the overall dataset, were General disorders and administration site conditions (51,335 AEs), Nervous system disorders (25,957), Musculoskeletal and connective tissue disorders (17,283), Gastrointestinal disorders (14,096), Skin and subcutaneous tissue disorders (8,476), Respiratory, thoracic and mediastinal disorders (8,848), Infections and infestations (4,610), Injury, poisoning and procedural complications (5,590), and Investigations (3,693).

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Figure 1. Total Number of BNT162b2 AEs by System Organ Classes and Event Seriousness

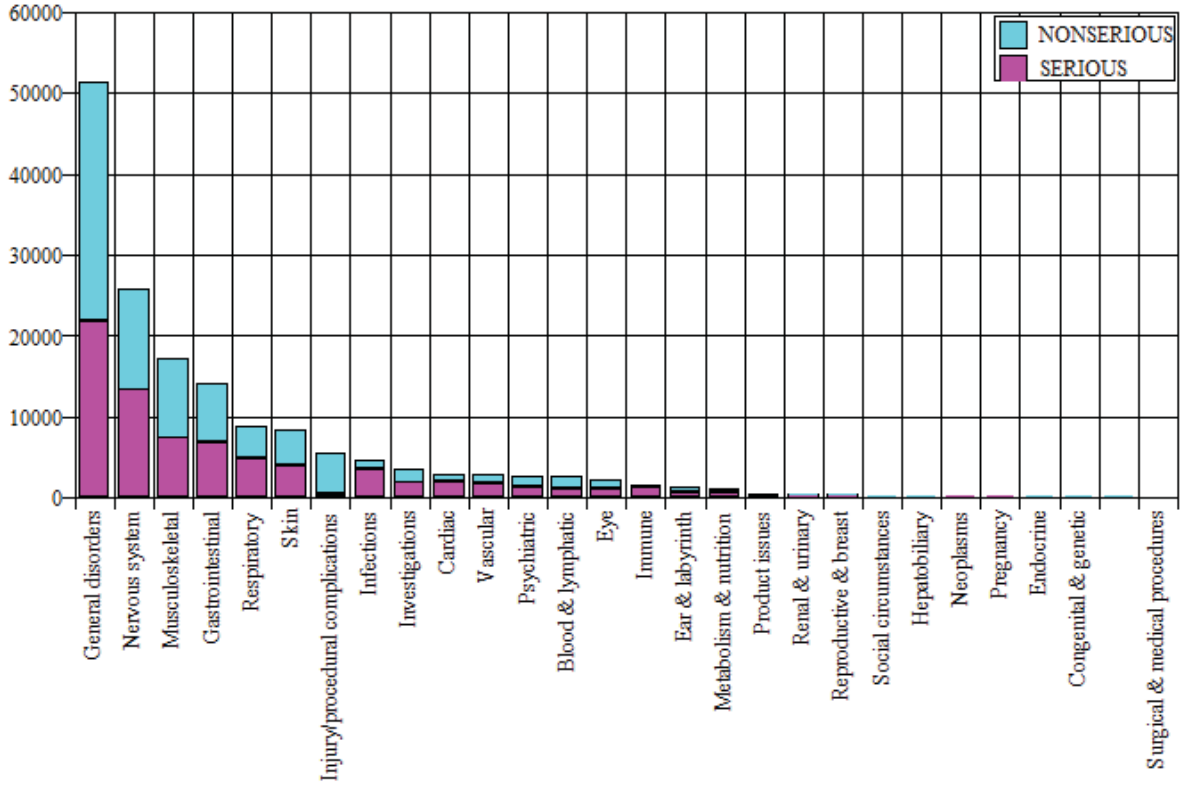

Table 2 shows the most commonly (≥2%) reported MedDRA (v. 23.1) PTs in the overall dataset (through 28 February 2021),

Table 2. Events Reported in ≥2% Cases

		Cumulatively Through 28 February 2021
MedDRA SOC	**MedDRA PT**	**AEs (AERP%) N = 42086**
Blood and lymphatic system disorders		
	Lymphadenopathy	1972 (4.7%)
Cardiac disorders		
	Tachycardia	1098 (2.6%)
Gastrointestinal disorders		
	Nausea	5182 (12.3%)
	Diarrhoea	1880 (4.5%)
	Vomiting	1698 (4.0%)
General disorders and administration site conditions		
	Pyrexia	7666 (18.2%)
	Fatigue	7338 (17.4%)
	Chills	5514 (13.1%)
	Vaccination site pain	5181 (12.3%)

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Table 2. Events Reported in ≥2% Cases

		Cumulatively Through 28 February 2021
MedDRA SOC	**MedDRA PT**	**AEs (AERP%) N = 42086**
	Pain	3691 (8.8%)
	Malaise	2897 (6.9%)
	Asthenia	2285 (5.4%)
	Drug ineffective	2201 (5.2%)
	Vaccination site erythema	930 (2.2%)
	Vaccination site swelling	913 (2.2%)
	Influenza like illness	835 (2%)
Infections and infestations		
	COVID-19	1927 (4.6%)
Injury, poisoning and procedural complications		
	Off label use	880 (2.1%)
	Product use issue	828 (2.0%)
Musculoskeletal and connective tissue disorders		
	Myalgia	4915 (11.7%)
	Pain in extremity	3959 (9.4%)
	Arthralgia	3525 (8.4%)
Nervous system disorders		
	Headache	10131 (24.1%)
	Dizziness	3720 (8.8%)
	Paraesthesia	1500 (3.6%)
	Hypoaesthesia	999 (2.4%)
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	2057 (4.9%)
	Cough	1146 (2.7%)
	Oropharyngeal pain	948 (2.3%)
Skin and subcutaneous tissue disorders		
	Pruritus	1447 (3.4%)
	Rash	1404 (3.3%)
	Erythema	1044 (2.5%)
	Hyperhidrosis	900 (2.1%)
	Urticaria	862 (2.1%)
Total number of events		**93473**

3.1.2. Summary of Safety Concerns in the US Pharmacovigilance Plan

Table 3. Safety concerns

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
Missing information	Use in Pregnancy and lactation Use in Paediatric Individuals <12 Years of Age Vaccine Effectiveness

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Table 4. Important Identified Risk

<table>
<tr><th>Topic</th><th>Description</th></tr>
<tr><td>Important Identified Risk</td><td>Post Authorization Cases Evaluation (cumulative to 28 Feb 2021)
Total Number of Cases in the Reporting Period (N=42086)</td></tr>
<tr><td>Anaphylaxis</td><td>Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 1833 potentially relevant cases were retrieved from the Anaphylactic reaction SMQ (Narrow and Broad) search strategy, applying the MedDRA algorithm. These cases were individually reviewed and assessed according to Brighton Collaboration (BC) definition and level of diagnostic certainty as shown in the Table below:
<table>
<tr><td>Brighton Collaboration Level</td><td>Number of cases</td></tr>
<tr><td>BC 1</td><td>290</td></tr>
<tr><td>BC 2</td><td>311</td></tr>
<tr><td>BC 3</td><td>10</td></tr>
<tr><td>BC 4</td><td>391</td></tr>
<tr><td>BC 5</td><td>831</td></tr>
<tr><td>Total</td><td>1833</td></tr>
</table>
Level 1 indicates a case with the highest level of diagnostic certainty of anaphylaxis, whereas the diagnostic certainty is lowest for Level 3. Level 4 is defined as “reported event of anaphylaxis with insufficient evidence to meet the case definition” and Level 5 as not a case of anaphylaxis.

There were 1002 cases (54.0% of the potentially relevant cases retrieved), 2958 potentially relevant events, from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy, meeting BC Level 1 to 4:

Country of incidence: UK (261), US (184), Mexico (99), Italy (82), Germany (67), Spain (38), France (36), Portugal (22), Denmark (20), Finland, Greece (19 each), Sweden (17), Czech Republic , Netherlands (16 each), Belgium, Ireland (13 each), Poland (12), Austria (11); the remaining 57 cases originated from 15 different countries.
Relevant event seriousness: Serious (2341), Non-Serious (617);
Gender: Females (876), Males (106), Unknown (20);
Age (n=961) ranged from 16 to 98 years (mean = 54.8 years, median = 42.5 years);
Relevant even outcome[a]: fatal (9)[b], resolved/resolving (1922), not resolved (229), resolved with sequelae (48), unknown (754);
Most frequently reported relevant PTs (≥2%), from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy: Anaphylactic reaction (435), Dyspnoea (356), Rash (190), Pruritus (175), Erythema (159), Urticaria (133), Cough (115), Respiratory distress, Throat tightness (97 each), Swollen tongue (93), Anaphylactic shock (80), Hypotension (72), Chest discomfort (71), Swelling face (70), Pharyngeal swelling (68), and Lip swelling (64).

Conclusion: Evaluation of BC cases Level 1 - 4 did not reveal any significant new safety information. Anaphylaxis is appropriately described in the product labeling as are non-anaphylactic hypersensitivity events. Surveillance will continue.</td></tr>
</table>

a Different clinical outcome may be reported for an event that occurred more than once to the same individual.
b There were 4 individuals in the anaphylaxis evaluation who died on the same day they were vaccinated. Although these patients experienced adverse events (9) that are potential symptoms of anaphylaxis, they all had serious underlying medical conditions, and one individual appeared to also have COVID-19 pneumonia, that likely contributed to their deaths

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Table 5. Important Potential Risk

Topic	Description
Important Potential Risk	**Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)**
Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	No post-authorized AE reports have been identified as cases of VAED/VAERD, therefore, there is no observed data at this time. An expected rate of VAED is difficult to establish so a meaningful observed/expected analysis cannot be conducted at this point based on available data. The feasibility of conducting such an analysis will be re-evaluated on an ongoing basis as data on the virus grows and the vaccine safety data continues to accrue. The search criteria utilised to identify potential cases of VAED for this report includes PTs indicating a lack of effect of the vaccine and PTs potentially indicative of severe or atypical COVID-19[a]. Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 138 cases [0.33% of the total PM dataset], reporting 317 potentially relevant events were retrieved: Country of incidence: UK (71), US (25), Germany (14), France, Italy, Mexico, Spain, (4 each), Denmark (3); the remaining 9 cases originated from 9 different countries; Cases Seriousness: 138; Seriousness criteria for the total 138 cases: Medically significant (71, of which 8 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (16, of which 1 also serious for disability), Life threatening (13, of which 7 were also serious for hospitalization), Death (38). Gender: Females (73), Males (57), Unknown (8); Age (n=132) ranged from 21 to 100 years (mean = 57.2 years, median = 59.5); Case outcome: fatal (38), resolved/resolving (26), not resolved (65), resolved with sequelae (1), unknown (8); Of the 317 relevant events, the most frequently reported PTs (≥2%) were: Drug ineffective (135), Dyspnoea (53), Diarrhoea (30), COVID-19 pneumonia (23), Vomiting (20), Respiratory failure (8), and Seizure (7). Conclusion: VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 37 subjects with suspected COVID-19 and 101 subjects with confirmed COVID-19 following one or both doses of the vaccine; 75 of the 101 cases were severe, resulting in hospitalisation, disability, life-threatening consequences or death. None of the 75 cases could be definitively considered as VAED/VAERD. In this review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERD remains a theoretical risk for the vaccine. Surveillance will continue.

a. Search criteria: Standard Decreased Therapeutic Response Search AND PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children.

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Table 6. Description of Missing Information

Topic	Description
Missing Information	**Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)**
Use in Pregnancy and lactation	• Number of cases: 413[a] (0.98% of the total PM dataset); 84 serious and 329 non-serious; • Country of incidence: US (205), UK (64), Canada (31), Germany (30), Poland (13), Israel (11); Italy (9), Portugal (8), Mexico (6), Estonia, Hungary and Ireland, (5 each), Romania (4), Spain (3), Czech Republic and France (2 each), the remaining 10 cases were distributed among 10 other countries. Pregnancy cases: 274 cases including: • 270 mother cases and 4 foetus/baby cases representing 270 unique pregnancies (the 4 foetus/baby cases were linked to 3 mother cases; 1 mother case involved twins). • Pregnancy outcomes for the 270 pregnancies were reported as spontaneous abortion (23), outcome pending (5), premature birth with neonatal death, spontaneous abortion with intrauterine death (2 each), spontaneous abortion with neonatal death, and normal outcome (1 each). No outcome was provided for 238 pregnancies (note that 2 different outcomes were reported for each twin, and both were counted). • 146 non-serious mother cases reported exposure to vaccine in utero without the occurrence of any clinical adverse event. The exposure PTs coded to the PTs Maternal exposure during pregnancy (111), Exposure during pregnancy (29) and Maternal exposure timing unspecified (6). Trimester of exposure was reported in 21 of these cases: 1st trimester (15 cases), 2nd trimester (7), and 3rd trimester (2). • 124 mother cases, 49 non-serious and 75 serious, reported clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases coded to the PTs Abortion spontaneous (25), Uterine contraction during pregnancy, Premature rupture of membranes, Abortion, Abortion missed, and Foetal death (1 each). Other clinical events which occurred in more than 5 cases coded to the PTs Headache (33), Vaccination site pain (24), Pain in extremity and Fatigue (22 each), Myalgia and Pyrexia (16 each), Chills (13) Nausea (12), Pain (11), Arthralgia (9), Lymphadenopathy and Drug ineffective (7 each), Chest pain, Dizziness and Asthenia (6 each), Malaise and COVID-19 (5 each). Trimester of exposure was reported in 22 of these cases: 1st trimester (19 cases), 2nd trimester (1 case), 3rd trimester (2 cases). • 4 serious foetus/baby cases reported the PTs Exposure during pregnancy, Foetal growth restriction, Maternal exposure during pregnancy, Premature baby (2 each), and Death neonatal (1). Trimester of exposure was reported for 2 cases (twins) as occurring during the 1st trimester. Breast feeding baby cases: 133, of which: • 116 cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical adverse events; • 17 cases, 3 serious and 14 non-serious, reported the following clinical events that occurred in the infant/child exposed to vaccine via breastfeeding: Pyrexia (5), Rash (4), Infant irritability (3), Infantile vomiting, Diarrhoea, Insomnia, and Illness (2 each), Poor feeding infant, Lethargy, Abdominal discomfort, Vomiting, Allergy to vaccine, Increased appetite, Anxiety, Crying, Poor quality sleep, Eructation, Agitation, Pain and Urticaria (1 each). Breast feeding mother cases (6): • 1 serious case reported 3 clinical events that occurred in a mother during breast feeding (PT Maternal exposure during breast feeding); these events coded to the PTs Chills, Malaise, and Pyrexia • 1 non-serious case reported with very limited information and without associated AEs.

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Table 6. Description of Missing Information

Topic	Description
Missing Information	**Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)**
	• In 4 cases (3 non-serious; 1 serious) Suppressed lactation occurred in a breast feeding women with the following co-reported events: Pyrexia (2), Paresis, Headache, Chills, Vomiting, Pain in extremity, Arthralgia, Breast pain, Scar pain, Nausea, Migraine, Myalgia, Fatigue and Breast milk discolouration (1 each). Conclusion: There were no safety signals that emerged from the review of these cases of use in pregnancy and while breast feeding.
Use in Paediatric Individuals <12 Years of Age	<u>Paediatric individuals <12 years of age</u> • Number of cases: 34[d] (0.1% of the total PM dataset), indicative of administration in paediatric subjects <12 years of age; • Country of incidence: UK (29), US (3), Germany and Andorra (1 each); • Cases Seriousness: Serious (24), Non-Serious (10); • Gender: Females (25), Males (7), Unknown (2); • Age (n=34) ranged from 2 months to 9 years, mean = 3.7 years, median = 4.0; • Case outcome: resolved/resolving (16), not resolved (13), and unknown (5). • Of the 132 reported events, those reported more than once were as follows: Product administered to patient of inappropriate age (27, see Medication Error), Off label use (11), Pyrexia (6), Product use issue (5), Fatigue, Headache and Nausea (4 each), Vaccination site pain (3), Abdominal pain upper, COVID-19, Facial paralysis, Lymphadenopathy, Malaise, Pruritus and Swelling (2 each). Conclusion: No new significant safety information was identified based on a review of these cases compared with the non-paediatric population.

Vaccine Effectiveness	Company conventions for coding cases indicative of lack of efficacy:
	
	The coding conventions for lack of efficacy in the context of administration of the COVID-19 vaccine were revised on 15 February 2021, as shown below:
	• PT "Vaccination failure" is coded when ALL of the following criteria are met:
	  o The subject has received the series of two doses per the dosing regimen in local labeling.
	  o At least 7 days have elapsed since the second dose of vaccine has been administered.
	  o The subject experiences SARS-CoV-2 infection (confirmed laboratory tests).
	• PT "Drug ineffective" is coded when either of the following applies:
	  o The infection is not confirmed as SARS-CoV-2 through laboratory tests (irrespective of the vaccination schedule). This includes scenarios where LOE is stated or implied, e.g., "the vaccine did not work", "I got COVID-19".
	  o It is unknown:
	  ▪ Whether the subject has received the series of two doses per the dosing regimen in local labeling;
	  ▪ How many days have passed since the first dose (including unspecified number of days like" a few days", "some days", etc.);
	  ▪ If 7 days have passed since the second dose;
	  o The subject experiences a vaccine preventable illness 14 days after receiving the first dose up to and through 6 days after receipt of the second dose.
	
	Note: after the immune system as had sufficient time (14 days) to respond to the vaccine, a report of COVID-19 is considered a potential lack of efficacy even if the vaccination course is not complete.
	
	Summary of the coding conventions for onset of vaccine preventable disease versus the vaccination date:

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Table 6. Description of Missing Information

Topic	Description
Missing Information	**Post Authorization Cases Evaluation (cumulative to 28 Feb 2021)** **Total Number of Cases in the Reporting Period (N=42086)**

1st dose (day 1-13)	From day 14 post 1st dose to day 6 post 2nd dose	Day 7 post 2nd dose
Code only the events describing the SARS-CoV-2 infection	Code "Drug ineffective"	Code "Vaccination failure"
Scenario Not considered LOE	Scenario considered LOE as "Drug ineffective"	Scenario considered LOE as "Vaccination failure"

Lack of efficacy cases

- Number of cases: 1665[b] (3.9 % of the total PM dataset) of which 1100 were medically confirmed and 565 non medically confirmed;
- Number of lack of efficacy events: 1665 [PT: Drug ineffective (1646) and Vaccination failure (19)[f]].
- Country of incidence: US (665), UK (405), Germany (181), France (85), Italy (58), Romania (47), Belgium (33), Israel (30), Poland (28), Spain (21), Austria (18), Portugal (17), Greece (15), Mexico (13), Denmark (8), Canada (7), Hungary, Sweden and United Arab Emirates (5 each), Czech Republic (4), Switzerland (3); the remaining 12 cases originated from 9 different countries.
- COVID-19 infection was suspected in 155 cases, confirmed in 228 cases, in 1 case it was reported that the first dose was not effective (no other information).
- COVID-19 infection (suspected or confirmed) outcome was reported as resolved/resolving (165), not resolved (205) or unknown (1230) at the time of the reporting; there were 65 cases where a fatal outcome was reported.

Drug ineffective cases (1649)

- Drug ineffective event seriousness: serious (1625), non-serious (21)[e];
- Lack of efficacy term was reported:
  - after the 1st dose in 788 cases
  - after the 2nd dose in 139 cases
  - in 722 cases it was unknown after which dose the lack of efficacy occurred.
- Latency of lack of efficacy term reported after the first dose was known for 176 cases:
  - Within 9 days: 2 subjects;
  - Within 14 and 21 days: 154 subjects;
  - Within 22 and 50 days: 20 subjects;
- Latency of lack of efficacy term reported after the second dose was known for 69 cases:
  - Within 0 and 7 days: 42 subjects;
  - Within 8 and 21 days: 22 subjects;
  - Within 23 and 36 days: 5 subjects.
- Latency of lack of efficacy term reported in cases where the number of doses administered was not provided, was known in 409 cases:
  - Within 0 and 7 days after vaccination: 281 subjects.
  - Within 8 and 14 days after vaccination: 89 subjects.
  - Within 15 and 44 days after vaccination: 39 subjects.

According to the RSI, individuals may not be fully protected until 7 days after their second dose of vaccine, therefore for the above 1649 cases where lack of efficacy was reported after the 1st dose or the

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Table 6. Description of Missing Information

Topic	Description
Missing Information	**Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)**
	2nd dose, the reported events may represent signs and symptoms of intercurrent or undiagnosed COVID-19 infection or infection in an individual who was not fully vaccinated, rather than vaccine ineffectiveness. ***Vaccination failure cases (16)*** • Vaccination failure seriousness: all serious; • Lack of efficacy term was reported in all cases after the 2nd dose: • Latency of lack of efficacy was known for 14 cases: o Within 7 and 13 days: 8 subjects; o Within 15 and 29 days: 6 subjects. COVID-19 (10) and Asymptomatic COVID-19 (6) were the reported vaccine preventable infections that occurred in these 16 cases. Conclusion: No new safety signals of vaccine lack of efficacy have emerged based on a review of these cases.

a. From a total of 417 cases, 4 cases were excluded from the analysis. In 3 cases, the MAH was informed that a 33-year-old and two unspecified age pregnant female patients were scheduled to receive bnt162b2 (PT reported Off label use and Product use issue in 2 cases; Circumstance or information capable of leading to medication error in one case). One case reported the PT Morning sickness; however, pregnancy was not confirmed in this case.
b. 558 additional cases retrieved in this dataset were excluded from the analysis; upon review, 546 cases cannot be considered true lack of efficacy cases because the PT Drug ineffective was coded but the subjects developed SARS-CoV-2 infection during the early days from the first dose (days 1 – 13); the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable disease during this time is not considered a potential lack of effect of the vaccine; in 5 cases the PT Drug ineffective was removed after data lock point (DLP) because the subjects did not develop COVID-19 infection; in 1 case, reporting Treatment failure and Transient ischaemic attack, the Lack of efficacy PT did not refer to BNT162b2 vaccine; 5 cases have been invalidated in the safety database after DLP; 1 case has been deleted from the discussion because the PTs reported Pathogen resistance and Product preparation issue were not indicative of a lack of efficacy. to be eliminated.
c. Upon review, 31 additional cases were excluded from the analysis as the data reported (e.g. clinical details, height, weight, etc.) were not consistent with paediatric subjects
d. Upon review, 28 additional cases were excluded from the analysis as the data reported (e.g. clinical details, height, weight, etc.) were not consistent with paediatric subjects.
e. Different clinical outcomes may be reported for an event that occurred more than once to the same individual
f. In 2 cases the PT Vaccination failure was replaced with Drug ineffective after DLP. Another case was not included in the discussion of the Vaccination failure cases because correct scheduling (21 days apart between the first and second dose) cannot be confirmed.

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3.1.3. Review of Adverse Events of Special Interest (AESIs)

Please refer to Appendix 1 for the list of the company's AESIs for BNT162b2.

The company's AESI list takes into consideration the lists of AESIs from the following expert groups and regulatory authorities: Brighton Collaboration (SPEAC), ACCESS protocol, US CDC (preliminary list of AESI for VAERS surveillance), MHRA (unpublished guideline).

The AESI terms are incorporated into a TME list and include events of interest due to their association with severe COVID-19 and events of interest for vaccines in general.

The AESI list is comprised of MedDRA PTs, HLTs, HLGTs or MedDRA SMQs and can be changed as appropriate based on the evolving safety profile of the vaccine.

Table 7 provides a summary review of cumulative cases within AESI categories in the Pfizer safety database. This is distinct from safety signal evaluations which are conducted and included, as appropriate, in the Summary Monthly Safety Reports submitted regularly to the FDA and other Health Authorities.

Table 7. AESIs Evaluation for BNT162b2

AESIs[a] **Category**	**Post-Marketing Cases Evaluation**[b] **Total Number of Cases (N=42086)**
Anaphylactic Reactions *Search criteria: Anaphylactic reaction SMQ (Narrow and Broad, with the algorithm applied), selecting relevant cases according to BC criteria*	Please refer to the Risk 'Anaphylaxis' included above in Table 4.
Cardiovascular AESIs *Search criteria: PTs Acute myocardial infarction; Arrhythmia; Cardiac failure; Cardiac failure acute; Cardiogenic shock; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia*	• Number of cases: 1403 (3.3% of the total PM dataset), of which 241 are medically confirmed and 1162 are non-medically confirmed; • Country of incidence: UK (268), US (233), Mexico (196), Italy (141), France (128), Germany (102), Spain (46), Greece (45), Portugal (37), Sweden (20), Ireland (17), Poland (16), Israel (13), Austria, Romania and Finland (12 each), Netherlands (11), Belgium and Norway (10 each), Czech Republic (9), Hungary and Canada (8 each), Croatia and Denmark (7 each), Iceland (5); the remaining 30 cases were distributed among 13 other countries; • Subjects' gender: female (1076), male (291) and unknown (36); • Subjects' age group (n = 1346): Adult[c] (1078), Elderly[d] (266) Child[e] and Adolescent[f] (1 each); • Number of relevant events: 1441, of which 946 serious, 495 non-serious; in the cases reporting relevant serious events; • Reported relevant PTs: Tachycardia (1098), Arrhythmia (102), Myocardial infarction (89), Cardiac failure (80), Acute myocardial infarction (41), Cardiac failure acute (11), Cardiogenic shock and Postural orthostatic tachycardia syndrome (7 each) and Coronary artery disease (6); • Relevant event onset latency (n = 1209): Range from <24 hours to 21 days, median <24 hours;

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] Category	Post-Marketing Cases Evaluation[b] Total Number of Cases (N=42086)
	• Relevant event outcome[g]: fatal (136), resolved/resolving (767), resolved with sequelae (21), not resolved (140) and unknown (380); Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
COVID-19 AESIs *Search criteria: Covid-19 SMQ (Narrow and Broad) OR PTs Ageusia; Anosmia*	• Number of cases: 3067 (7.3% of the total PM dataset), of which 1013 are medically confirmed and 2054 are non-medically confirmed; • Country of incidence: US (1272), UK (609), Germany (360), France (161), Italy (94), Spain (69), Romania (62), Portugal (51), Poland (50), Mexico (43), Belgium (42), Israel (41), Sweden (30), Austria (27), Greece (24), Denmark (18), Czech Republic and Hungary (17 each), Canada (12), Ireland (11), Slovakia (9), Latvia and United Arab Emirates (6 each); the remaining 36 cases were distributed among 16 other different countries; • Subjects' gender: female (1650), male (844) and unknown (573); • Subjects' age group (n= 1880): Adult (1315), Elderly (560), Infant[h] and Adolescent (2 each), Child (1); • Number of relevant events: 3359, of which 2585 serious, 774 non-serious; • Most frequently reported relevant PTs (>1 occurrence): COVID-19 (1927), SARS-CoV-2 test positive (415), Suspected COVID-19 (270), Ageusia (228), Anosmia (194), SARS-CoV-2 antibody test negative (83), Exposure to SARS-CoV-2 (62), SARS-CoV-2 antibody test positive (53), COVID-19 pneumonia (51), Asymptomatic COVID-19 (31), Coronavirus infection (13), Occupational exposure to SARS-CoV-2 (11), SARS-CoV-2 test false positive (7), Coronavirus test positive (6), SARS-CoV-2 test negative (3) SARS-CoV-2 antibody test (2); • Relevant event onset latency (n = 2070): Range from <24 hours to 374 days, median 5 days; • Relevant event outcome: fatal (136), not resolved (547), resolved/resolving (558), resolved with sequelae (9) and unknown (2110). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Dermatological AESIs *Search criteria: PT Chillblains; Erythema multiforme*	• Number of cases: 20 cases (0.05% of the total PM dataset), of which 15 are medically confirmed and 5 are non-medically confirmed; • Country of incidence: UK (8), France and Poland (2 each), and the remaining 8 cases were distributed among 8 other different countries; • Subjects' gender: female (17) male and unknown (1 each); • Subjects' age group (n=19): Adult (18), Elderly (1); • Number of relevant events: 20 events, 16 serious, 4 non-serious

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] Category	Post-Marketing Cases Evaluation[b] Total Number of Cases (N=42086)
	• Reported relevant PTs: Erythema multiforme (13) and Chillblains (7) • Relevant event onset latency (n = 18): Range from <24 hours to 17 days, median 3 days; • Relevant event outcome: resolved/resolving (7), not resolved (8) and unknown (6). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Haematological AESIs *Search criteria: Leukopenias NEC (HLT) (Primary Path) OR Neutropenias (HLT) (Primary Path) OR PTs Immune thrombocytopenia, Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms*	• Number of cases: 932 (2.2 % of the total PM dataset), of which 524 medically confirmed and 408 non-medically confirmed; • Country of incidence: UK (343), US (308), France (50), Germany (43), Italy (37), Spain (27), Mexico and Poland (13 each), Sweden (10), Israel (9), Netherlands (8), Denmark, Finland, Portugal and Ireland (7 each), Austria and Norway (6 each), Croatia (4), Greece, Belgium, Hungary and Switzerland (3 each), Cyprus, Latvia and Serbia (2 each); the remaining 9 cases originated from 9 different countries; • Subjects' gender (n=898): female (676) and male (222); • Subjects' age group (n=837): Adult (543), Elderly (293), Infant (1); • Number of relevant events: 1080, of which 681 serious, 399 non-serious; • Most frequently reported relevant PTs (≥15 occurrences) include: Epistaxis (127), Contusion (112), Vaccination site bruising (96), Vaccination site haemorrhage (51), Petechiae (50), Haemorrhage (42), Haematochezia (34), Thrombocytopenia (33), Vaccination site haematoma (32), Conjunctival haemorrhage and Vaginal haemorrhage (29 each), Haematoma, Haemoptysis and Menorrhagia (27 each), Haematemesis (25), Eye haemorrhage (23), Rectal haemorrhage (22), Immune thrombocytopenia (20), Blood urine present (19), Haematuria, Neutropenia and Purpura (16 each) Diarrhoea haemorrhagic (15); • Relevant event onset latency (n = 787): Range from <24 hours to 33 days, median = 1 day; • Relevant event outcome: fatal (34), resolved/resolving (393), resolved with sequelae (17), not resolved (267) and unknown (371). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Hepatic AESIs *Search criteria: Liver related investigations, signs and symptoms (SMQ) (Narrow and Broad) OR PT Liver injury*	• Number of cases: 70 cases (0.2% of the total PM dataset), of which 54 medically confirmed and 16 non-medically confirmed; • Country of incidence: UK (19), US (14), France (7), Italy (5), Germany (4), Belgium, Mexico and Spain (3 each), Austria, and Iceland (2 each); the remaining 8 cases originated from 8 different countries; • Subjects' gender: female (43), male (26) and unknown (1); • Subjects' age group (n=64): Adult (37), Elderly (27);

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] Category	Post-Marketing Cases Evaluation[b] Total Number of Cases (N=42086)
	• Number of relevant events: 94, of which 53 serious, 41 non-serious; • Most frequently reported relevant PTs (≥3 occurrences) include: Alanine aminotransferase increased (16), Transaminases increased and Hepatic pain (9 each), Liver function test increased (8), Aspartate aminotransferase increased and Liver function test abnormal (7 each), Gamma-glutamyltransferase increased and Hepatic enzyme increased (6 each), Blood alkaline phosphatase increased and Liver injury (5 each), Ascites, Blood bilirubin increased and Hypertransaminasaemia (3 each); • Relevant event onset latency (n = 57): Range from <24 hours to 20 days, median 3 days; • Relevant event outcome: fatal (5), resolved/resolving (27), resolved with sequelae (1), not resolved (14) and unknown (47). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Facial Paralysis *Search criteria: PTs Facial paralysis, Facial paresis*	• Number of cases: 449[i] (1.07% of the total PM dataset), 314 medically confirmed and 135 non-medically confirmed; • Country of incidence: US (124), UK (119), Italy (40), France (27), Israel (20), Spain (18), Germany (13), Sweden (11), Ireland (9), Cyprus (8), Austria (7), Finland and Portugal (6 each), Hungary and Romania (5 each), Croatia and Mexico (4 each), Canada (3),Czech Republic, Malta, Netherlands, Norway, Poland and Puerto Rico (2 each); the remaining 8 cases originated from 8 different countries; • Subjects' gender: female (295), male (133), unknown (21); • Subjects' age group (n=411): Adult (313), Elderly (96), Infant[j] and Child (1 each); • Number of relevant events[k]: 453, of which 399 serious, 54 non-serious; • Reported relevant PTs: Facial paralysis (401), Facial paresis (64); • Relevant event onset latency (n = 404): Range from <24 hours to 46 days, median 2 days; • Relevant event outcome: resolved/resolving (184), resolved with sequelae (3), not resolved (183) and unknown (97); Overall Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue. Causality assessment will be further evaluated following availability of additional unblinded data from the clinical study C4591001, which will be unblinded for final analysis approximately mid-April 2021. Additionally, non-interventional post-authorisation safety studies, C4591011 and C4591012 are expected to capture data on a sufficiently large vaccinated population to detect an increased risk of Bell's palsy in vaccinated individuals. The timeline for conducting these analyses will be established based on the size of the vaccinated population captured in the study data sources by the first interim reports (due 30 June

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] **Category**	**Post-Marketing Cases Evaluation**[b] **Total Number of Cases (N=42086)**
	2021). Study C4591021, pending protocol endorsement by EMA, is also intended to inform this risk.
Immune-Mediated/Autoimmune AESIs *Search criteria: Immune-mediated/autoimmune disorders (SMQ) (Broad and Narrow) OR Autoimmune disorders HLGT (Primary Path) OR PTs Cytokine release syndrome; Cytokine storm; Hypersensitivity*	• Number of cases: 1050 (2.5 % of the total PM dataset), of which 760 medically confirmed and 290 non-medically confirmed; • Country of incidence (>10 cases): UK (267), US (257), Italy (70), France and Germany (69 each), Mexico (36), Sweden (35), Spain (32), Greece (31), Israel (21), Denmark (18), Portugal (17), Austria and Czech Republic (16 each), Canada (12), Finland (10). The remaining 74 cases were from 24 different countries. • Subjects' gender (n=682): female (526), male (156). • Subjects' age group (n=944): Adult (746), Elderly (196), Adolescent (2). • Number of relevant events: 1077, of which 780 serious, 297 non-serious. • Most frequently reported relevant PTs (>10 occurrences): Hypersensitivity (596), Neuropathy peripheral (49), Pericarditis (32), Myocarditis (25), Dermatitis (24), Diabetes mellitus and Encephalitis (16 each), Psoriasis (14), Dermatitis Bullous (13), Autoimmune disorder and Raynaud's phenomenon (11 each); • Relevant event onset latency (n = 807): Range from <24 hours to 30 days, median <24 hours. • Relevant event outcome[l]: resolved/resolving (517), not resolved (215), fatal (12), resolved with sequelae (22) and unknown (312). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Musculoskeletal AESIs *Search criteria: PTs Arthralgia; Arthritis; Arthritis bacterial*[n]*; Chronic fatigue syndrome; Polyarthritis; Polyneuropathy; Post viral fatigue syndrome; Rheumatoid arthritis*	• Number of cases: 3600 (8.5% of the total PM dataset), of which 2045 medically confirmed and 1555 non-medically confirmed; • Country of incidence: UK (1406), US (1004), Italy (285), Mexico (236), Germany (72), Portugal (70), France (48), Greece and Poland (46), Latvia (33), Czech Republic (32), Israel and Spain (26), Sweden (25), Romania (24), Denmark (23), Finland and Ireland (19 each), Austria and Belgium (18 each), Canada (16), Netherlands (14), Bulgaria (12), Croatia and Serbia (9 each), Cyprus and Hungary (8 each), Norway (7), Estonia and Puerto Rico (6 each), Iceland and Lithuania (4 each); the remaining 21 cases originated from 11 different countries; • Subjects' gender (n=3471): female (2760), male (711); • Subjects' age group (n=3372): Adult (2850), Elderly (515), Child (4), Adolescent (2), Infant (1); • Number of relevant events: 3640, of which 1614 serious, 2026 non-serious; • Reported relevant PTs: Arthralgia (3525), Arthritis (70), Rheumatoid arthritis (26), Polyarthritis (5), Polyneuropathy, Post viral fatigue syndrome, Chronic fatigue syndrome (4 each), Arthritis bacterial (1); • Relevant event onset latency (n = 2968): Range from <24 hours to 32 days, median 1 day;

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] Category	Post-Marketing Cases Evaluation[b] Total Number of Cases (N=42086)
	• Relevant event outcome: resolved/resolving (1801), not resolved (959), resolved with sequelae (49), and unknown (853). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Neurological AESIs (including demyelination) *Search criteria: Convulsions (SMQ) (Broad and Narrow) OR Demyelination (SMQ) (Broad and Narrow) OR PTs Ataxia; Cataplexy; Encephalopathy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Narcolepsy*	• Number of cases: 501 (1.2% of the total PM dataset), of which 365 medically confirmed and 136 non-medically confirmed. • Country of incidence (≥9 cases): UK (157), US (68), Germany (49), Mexico (35), Italy (31), France (25), Spain (18), Poland (17), Netherlands and Israel (15 each), Sweden (9). The remaining 71 cases were from 22 different countries. • Subjects' gender (n=478): female (328), male (150). • Subjects' age group (n=478): Adult (329), Elderly (149); • Number of relevant events: 542, of which 515 serious, 27 non-serious. • Most frequently reported relevant PTs (>2 occurrences) included: Seizure (204), Epilepsy (83), Generalised tonic-clonic seizure (33), Guillain-Barre syndrome (24), Fibromyalgia and Trigeminal neuralgia (17 each), Febrile convulsion, (15), Status epilepticus (12), Aura and Myelitis transverse (11 each), Multiple sclerosis relapse and Optic neuritis (10 each), Petit mal epilepsy and Tonic convulsion (9 each), Ataxia (8), Encephalopathy and Tonic clonic movements (7 each), Foaming at mouth (5), Multiple sclerosis, Narcolepsy and Partial seizures (4 each), Bad sensation, Demyelination, Meningitis, Postictal state, Seizure like phenomena and Tongue biting (3 each); • Relevant event onset latency (n = 423): Range from <24 hours to 48 days, median 1 day; • Relevant events outcome: fatal (16), resolved/resolving (265), resolved with sequelae (13), not resolved (89) and unknown (161); Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Other AESIs *Search criteria: Herpes viral infections (HLT) (Primary Path) OR PTs Adverse event following immunisation; Inflammation; Manufacturing laboratory analytical testing issue; Manufacturing materials issue; Manufacturing production issue; MERS-CoV test; MERS-CoV test negative; MERS-CoV test positive; Middle East respiratory syndrome; Multiple organ dysfunction syndrome; Occupational exposure to communicable disease; Patient*	• Number of cases: 8152 (19.4% of the total PM dataset), of which 4977 were medically confirmed and 3175 non-medically confirmed; • Country of incidence (> 20 occurrences): UK (2715), US (2421), Italy (710), Mexico (223), Portugal (210), Germany (207), France (186), Spain (183), Sweden (133), Denmark (127), Poland (120), Greece (95), Israel (79), Czech Republic (76), Romania (57), Hungary (53), Finland (52), Norway (51), Latvia (49), Austria (47), Croatia (42), Belgium (41), Canada (39), Ireland (34), Serbia (28), Iceland (25), Netherlands (22). The remaining 127 cases were from 21 different countries; • Subjects' gender (n=7829): female (5969), male (1860); • Subjects' age group (n=7479): Adult (6330), Elderly (1125), Adolescent, Child (9 each), Infant (6);

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] Category	Post-Marketing Cases Evaluation[b] Total Number of Cases (N=42086)
isolation; Product availability issue; Product distribution issue; Product supply issue; Pyrexia; Quarantine; SARS-CoV-1 test; SARS-CoV-1 test negative; SARS-CoV-1 test positive	• Number of relevant events: 8241, of which 3674 serious, 4568 non-serious; • Most frequently reported relevant PTs (≥6 occurrences) included: Pyrexia (7666), Herpes zoster (259), Inflammation (132), Oral herpes (80), Multiple organ dysfunction syndrome (18), Herpes virus infection (17), Herpes simplex (13), Ophthalmic herpes zoster (10), Herpes ophthalmic and Herpes zoster reactivation (6 each); • Relevant event onset latency (n =6836): Range from <24 hours to 61 days, median 1 day; • Relevant events outcome: fatal (96), resolved/resolving (5008), resolved with sequelae (84), not resolved (1429) and unknown (1685). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Pregnancy Related AESIs *Search criteria: PTs Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Stillbirth; Uterine rupture; Vasa praevia*	For relevant cases, please refer to Table 6, Description of Missing Information, *Use in Pregnancy and While Breast Feeding*
Renal AESIs *Search criteria: PTs Acute kidney injury; Renal failure.*	• Number of cases: 69 cases (0.17% of the total PM dataset), of which 57 medically confirmed, 12 non-medically confirmed; • Country of incidence: Germany (17), France and UK (13 each), US (6), Belgium, Italy and Spain (4 each), Sweden (2), Austria, Canada, Denmark, Finland, Luxembourg and Norway (1 each); • Subjects' gender: female (46), male (23); • Subjects' age group (n=68): Adult (7), Elderly (60), Infant (1); • Number of relevant events: 70, all serious; • Reported relevant PTs: Acute kidney injury (40) and Renal failure (30); • Relevant event onset latency (n = 42): Range from <24 hours to 15 days, median 4 days; • Relevant event outcome: fatal (23), resolved/resolving (10), not resolved (15) and unknown (22). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Respiratory AESIs *Search criteria: Lower respiratory tract infections NEC (HLT)*	• Number of cases: 130 cases (0.3% of the total PM dataset), of which 107 medically confirmed;

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] **Category**	**Post-Marketing Cases Evaluation**[b] **Total Number of Cases (N=42086)**
(Primary Path) OR Respiratory failures (excl neonatal) (HLT) (Primary Path) OR Viral lower respiratory tract infections (HLT) (Primary Path) OR PTs: Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Pulmonary haemorrhage; Respiratory disorder; Severe acute respiratory syndrome	• Countries of incidence: United Kingdom (20), France (18), United States (16), Germany (14), Spain (13), Belgium and Italy (9), Denmark (8), Norway (5), Czech Republic, Iceland (3 each); the remaining 12 cases originated from 8 different countries. • Subjects' gender (n=130): female (72), male (58). • Subjects's age group (n=126): Elderly (78), Adult (47), Adolescent (1). • Number of relevant events: 137, of which 126 serious, 11 non-serious; • Reported relevant PTs: Respiratory failure (44), Hypoxia (42), Respiratory disorder (36), Acute respiratory distress syndrome (10), Chronic respiratory syndrome (3), Severe acute respiratory syndrome (2). • Relevant event onset latency (n=102): range from < 24 hours to 18 days, median 1 day; • Relevant events outcome: fatal (41), Resolved/resolving (47), not recovered (18) and unknown (31). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Thromboembolic Events *Search criteria: Embolism and thrombosis (HLGT) (Primary Path), excluding PTs reviewed as Stroke AESIs, OR PTs Deep vein thrombosis; Disseminated intravascular coagulation; Embolism; Embolism venous; Pulmonary embolism*	• Number of cases: 151 (0.3% of the total PM dataset), of which 111 medically confirmed and 40 non-medically confirmed; • Country of incidence: UK (34), US (31), France (20), Germany (15), Italy and Spain (6 each), Denmark and Sweden (5 each), Austria, Belgium and Israel (3 each), Canada, Cyprus, Netherlands and Portugal (2 each); the remaining 12 cases originated from 12 different countries; • Subjects' gender (n= 144): female (89), male (55); • Subjects' age group (n=136): Adult (66), Elderly (70); • Number of relevant events: 168, of which 165 serious, 3 non-serious; • Most frequently reported relevant PTs (>1 occurrence) included: Pulmonary embolism (60), Thrombosis (39), Deep vein thrombosis (35), Thrombophlebitis superficial (6), Venous thrombosis limb (4), Embolism, Microembolism, Thrombophlebitis and Venous thrombosis (3 each) Blue toe syndrome (2); • Relevant event onset latency (n = 124): Range from <24 hours to 28 days, median 4 days; • Relevant event outcome: fatal (18), resolved/resolving (54), resolved with sequelae (6), not resolved (49) and unknown (42). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Stroke *Search criteria: HLT Central nervous system haemorrhages and cerebrovascular accidents*	• Number of cases: 275 (0.6% of the total PM dataset), of which 180 medically confirmed and 95 non-medically confirmed; • Country of incidence: UK (81), US (66), France (32), Germany (21), Norway (14), Netherlands and Spain (11 each), Sweden (9),

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] **Category**	**Post-Marketing Cases Evaluation**[b] **Total Number of Cases (N=42086)**

(Primary Path) OR HLT Cerebrovascular venous and sinus thrombosis (Primary Path)	Israel (6), Italy (5), Belgium (3), Denmark, Finland, Poland and Switzerland (2 each); the remaining 8 cases originated from 8 different countries;
	• Subjects' gender (n= 273): female (182), male (91);
	• Subjects' age group (n=265): Adult (59), Elderly (205), Child[m] (1);
	• Number of relevant events: 300, all serious;
	• Most frequently reported relevant PTs (>1 occurrence) included:
	  o PTs indicative of Ischaemic stroke: Cerebrovascular accident (160), Ischaemic stroke (41), Cerebral infarction (15), Cerebral ischaemia, Cerebral thrombosis, Cerebral venous sinus thrombosis, Ischaemic cerebral infarction and Lacunal infarction (3 each) Basal ganglia stroke, Cerebellar infarction and Thrombotic stroke (2 each);
	  o PTs indicative of Haemorrhagic stroke: Cerebral haemorrhage (26), Haemorrhagic stroke (11), Haemorrhage intracranical and Subarachnoid haemorrhage (5 each), Cerebral haematoma (4), Basal ganglia haemorrhage and Cerebellar haemorrhage (2 each);
	• Relevant event onset latency (n = 241): Range from <24 hours to 41 days, median 2 days;
	• Relevant event outcome: fatal and resolved/resolving (61 each), resolved with sequelae (10), not resolved (85) and unknown (83).
	
	Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.

Vasculitic Events *Search criteria: Vasculitides HLT*	• Number of cases: 32 cases (0.08% of the total PM dataset), of which 26 medically confirmed and 6 non-medically confirmed; • Country of incidence: UK (13), France (4), Portugal, US and Spain (3 each), Cyprus, Germany, Hungary, Italy and Slovakia and Costa rica (1 each); • Subjects' gender: female (26), male (6); • Subjects' age group (n=31): Adult (15), Elderly (16); • Number of relevant events: 34, of which 25 serious, 9 non-serious; • Reported relevant PTs: Vasculitis (14), Cutaneous vasculitis and Vasculitic rash (4 each), (3), Giant cell arteritis and Peripheral ischaemia (3 each), Behcet's syndrome and Hypersensitivity vasculitis (2 each) Palpable purpura, and Takayasu's arteritis (1 each); • Relevant event onset latency (n = 25): Range from <24 hours to 19 days, median 3 days; • Relevant event outcome: fatal (1), resolved/resolving (13), not resolved (12) and unknown (8). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue

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Table 7. AESIs Evaluation for BNT162b2

AESIs[a] Category	Post-Marketing Cases Evaluation[b] Total Number of Cases (N=42086)

a. For the complete list of the AESIs, please refer to Appendix 5;
b. Please note that this corresponds to evidence from post-EUA/conditional marketing authorisation approval data sources;
c. Subjects with age ranged between 18 and 64 years;
d. Subjects with age equal to or above 65 years;
e. Subjects with age ranged between 2 and 11 years;
f. Subjects with age ranged between 12 and less than 18 years;
g. Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events;
h. Subjects with age ranged between 1 (28 days) and 23 months;
i. Twenty-four additional cases were excluded from the analysis as they were not cases of peripheral facial nerve palsy because they described other disorders (stroke, cerebral haemorrhage or transient ischaemic attack); 1 case was excluded from the analysis because it was invalid due to an unidentifiable reporter;
j. This UK case report received from the UK MHRA described a 1-year-old subject who received the vaccine, and had left postauricular ear pain that progressed to left-sided Bell's palsy 1 day following vaccination that had not resolved at the time of the report;
k. If a case included both PT Facial paresis and PT Facial paralysis, only the PT Facial paralysis was considered in the descriptions of the events as it is most clinically important;
l. Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events
m. This UK case report received from the UK MHRA described a 7-year-old female subject who received the vaccine and had stroke (unknown outcome); no follow-up is possible for clarification.
n. This PT not included in the AESIs/TME list was included in the review as relevant for ACCESS protocol criteria;

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3.1.4. Medication error

Cases potentially indicative of medication errors[1] that cumulatively occurred are summarized below.

- Number of relevant medication error cases: 2056[2] (4.9%) of which 1569 (3.7%) are medically confirmed.
- Number of relevant events: 2792
- Top 10 countries of incidence:
  - US (1201), France (171), UK (138), Germany (88), Czech Republic (87), Sweden (49), Israel (45), Italy (42), Canada (35), Romania (33), Finland (21), Portugal (20), Norway (14), Puerto Rico (13), Poland (12), Austria and Spain (10 each).

  Medication error case outcomes:

  - Fatal (7)[3],
  - Recovered/recovering (354, of which 4 are serious),
  - Recovered with sequelae (8, of which 3 serious)

[1] MedDRA (version 23.1) Higher Level Terms: Accidental exposures to product; Product administration errors and issues; Product confusion errors and issues; Product dispensing errors and issues; Product label issues; Product monitoring errors and issues; Product preparation errors and issues; Product selection errors and issues; Product storage errors and issues in the product use system; Product transcribing errors and communication issues, OR Preferred Terms: Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage process.

[2] Thirty-five (35) cases were exclude from the analysis because describing medication errors occurring in an unspecified number of individuals or describing medication errors occurring with co suspects were determined to be non-contributory.

[3] All the medication errors reported in these cases were assessed as non-serious occurrences with an unknown outcome; based on the available information including the causes of death, the relationship between the medication error and the death is weak. .

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- Not recovered (189, of which 84 are serious),
- Unknown (1498, of which 33 are serious).

1371 cases reported only MEs without any associated clinical adverse event. The PTs most frequently reported (≥12 occurrences) were: Poor quality product administered (539), Product temperature excursion issue (253), Inappropriate schedule of product administration (225), Product preparation error (206), Underdose (202), Circumstance or information capable of leading to medication error (120), Product preparation issue (119), Wrong technique in product usage process (76), Incorrect route of product administration (66), Accidental overdose (33), Product administered at inappropriate site (27), Incorrect dose administered and Accidental exposure to the product (25 each), Exposure via skin contact (22), Wrong product administered (17), Incomplete course of vaccination, and Product administration error (14 each) Product administered to patient of inappropriate age (12).

In 685 cases, there were co-reported AEs. The most frequently co- associated AEs (> 40 occurrences) were: Headache (187), Pyrexia (161), Fatigue (135), Chills (127), Pain (107), Vaccination site pain (100), Nausea (89), Myalgia (88), Pain in extremity (85) Arthralgia (68), Off label use (57), Dizziness (52), Lymphadenopathy (47), Asthenia (46) and Malaise (41). These cases are summarized in Table 8.

Table 8. ME PTs by seriousness with or without harm co-association (Through 28 February 2021)

	Serious		Non-Serious	
ME PTs	**With Harm**	**Without Harm**	**With Harm**	**Without Harm**
Accidental exposure to product	0	0	0	5
Accidental overdose	4	1	9	6
Booster dose missed	0	0	0	1
Circumstance or information capable of leading to medication error	0	0	5	11
Contraindicated product administered	1	0	0	2
Expired product administered	0	0	0	2
Exposure via skin contact	0	0	0	5
Inappropriate schedule of product administration	0	2	8	264
Incorrect dose administered	1	1	0	0

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Table 8. ME PTs by seriousness with or without harm co-association (Through 28 February 2021)

	Serious		Non-Serious	
ME PTs	**With Harm**	**Without Harm**	**With Harm**	**Without Harm**
Incorrect route of product administration	2	6	16	127
Lack of vaccination site rotation	1	0	0	0
Medication error	0	0	0	1
Poor quality product administered	1	0	0	34
Product administered at inappropriate site	2	1	13	29
Product administered to patient of inappropriate age	0	4	0	40
Product administration error	1	0	0	3
Product dose omission issue	0	1	0	3
Product preparation error	1	0	4	11
Product preparation issue	1	1	0	14

Overall, there were 68 cases with co-reported AEs reporting Harm and 599 cases with co-reported AEs without harm. Additionally, Intercepted medication errors was reported in 1 case (PTs Malaise, clinical outcome unknow) and Potential medication errors were reported in 17 cases.

4. DISCUSSION

Pfizer performs frequent and rigorous signal detection on BNT162b2 cases. The findings of these signal detection analyses are consistent with the known safety profile of the vaccine. This cumulative analysis to support the Biologics License Application for BNT162b2, is an integrated analysis of post-authorization safety data, from U.S. and foreign experience, focused on Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in the Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). The data do not reveal any novel safety concerns or risks requiring label changes and support a favorable benefit risk profile of to the BNT162b2 vaccine.

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5. SUMMARY AND CONCLUSION

Review of the available data for this cumulative PM experience, confirms a favorable benefit: risk balance for BNT162b2.

Pfizer will continue routine pharmacovigilance activities on behalf of BioNTech according to the Pharmacovigilance Agreement in place, in order to assure patient safety and will inform the Agency if an evaluation of the safety data yields significant new information for BNT162b2.

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APPENDIX 1. LIST OF ADVERSE EVENTS OF SPECIAL INTEREST

1p36 deletion syndrome;2-Hydroxyglutaric aciduria;5'nucleotidase increased;Acoustic neuritis;Acquired C1 inhibitor deficiency;Acquired epidermolysis bullosa;Acquired epileptic aphasia;Acute cutaneous lupus erythematosus;Acute disseminated encephalomyelitis;Acute encephalitis with refractory, repetitive partial seizures;Acute febrile neutrophilic dermatosis;Acute flaccid myelitis;Acute haemorrhagic leukoencephalitis;Acute haemorrhagic oedema of infancy;Acute kidney injury;Acute macular outer retinopathy;Acute motor axonal neuropathy;Acute motor-sensory axonal neuropathy;Acute myocardial infarction;Acute respiratory distress syndrome;Acute respiratory failure;Addison's disease;Administration site thrombosis;Administration site vasculitis;Adrenal thrombosis;Adverse event following immunisation;Ageusia;Agranulocytosis;Air embolism;Alanine aminotransferase abnormal;Alanine aminotransferase increased;Alcoholic seizure;Allergic bronchopulmonary mycosis;Allergic oedema;Alloimmune hepatitis;Alopecia areata;Alpers disease;Alveolar proteinosis;Ammonia abnormal;Ammonia increased;Amniotic cavity infection;Amygdalohippocampectomy;Amyloid arthropathy;Amyloidosis;Amyloidosis senile;Anaphylactic reaction;Anaphylactic shock;Anaphylactic transfusion reaction;Anaphylactoid reaction;Anaphylactoid shock;Anaphylactoid syndrome of pregnancy;Angioedema;Angiopathic neuropathy;Ankylosing spondylitis;Anosmia;Antiacetylcholine receptor antibody positive;Anti-actin antibody positive;Anti-aquaporin-4 antibody positive;Anti-basal ganglia antibody positive;Anti-cyclic citrullinated peptide antibody positive;Anti-epithelial antibody positive;Anti-erythrocyte antibody positive;Anti-exosome complex antibody positive;Anti-GAD antibody negative;Anti-GAD antibody positive;Anti-ganglioside antibody positive;Antigliadin antibody positive;Anti-glomerular basement membrane antibody positive;Anti-glomerular basement membrane disease;Anti-glycyl-tRNA synthetase antibody positive;Anti-HLA antibody test positive;Anti-IA2 antibody positive;Anti-insulin antibody increased;Anti-insulin antibody positive;Anti-insulin receptor antibody increased;Anti-insulin receptor antibody positive;Anti-interferon antibody negative;Anti-interferon antibody positive;Anti-islet cell antibody positive;Antimitochondrial antibody positive;Anti-muscle specific kinase antibody positive;Anti-myelin-associated glycoprotein antibodies positive;Anti-myelin-associated glycoprotein associated polyneuropathy;Antimyocardial antibody positive;Anti-neuronal antibody positive;Antineutrophil cytoplasmic antibody increased;Antineutrophil cytoplasmic antibody positive;Anti-neutrophil cytoplasmic antibody positive vasculitis;Anti-NMDA antibody positive;Antinuclear antibody increased;Antinuclear antibody positive;Antiphospholipid antibodies positive;Antiphospholipid syndrome;Anti-platelet antibody positive;Anti-prothrombin antibody positive;Antiribosomal P antibody positive;Anti-RNA polymerase III antibody positive;Anti-saccharomyces cerevisiae antibody test positive;Anti-sperm antibody positive;Anti-SRP antibody positive;Antisynthetase syndrome;Anti-thyroid antibody positive;Anti-transglutaminase antibody increased;Anti-VGCC antibody positive;Anti-VGKC antibody positive;Anti-vimentin antibody positive;Antiviral prophylaxis;Antiviral treatment;Anti-zinc transporter 8 antibody positive;Aortic embolus;Aortic thrombosis;Aortitis;Aplasia pure red cell;Aplastic anaemia;Application site thrombosis;Application site vasculitis;Arrhythmia;Arterial bypass occlusion;Arterial bypass thrombosis;Arterial thrombosis;Arteriovenous fistula thrombosis;Arteriovenous graft site stenosis;Arteriovenous graft thrombosis;Arteritis;Arteritis

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coronary;Arthralgia;Arthritis;Arthritis enteropathic;Ascites;Aseptic cavernous sinus thrombosis;Aspartate aminotransferase abnormal;Aspartate aminotransferase increased;Aspartate-glutamate-transporter deficiency;AST to platelet ratio index increased;AST/ALT ratio abnormal;Asthma;Asymptomatic COVID-19;Ataxia;Atheroembolism;Atonic seizures;Atrial thrombosis;Atrophic thyroiditis;Atypical benign partial epilepsy;Atypical pneumonia;Aura;Autoantibody positive;Autoimmune anaemia;Autoimmune aplastic anaemia;Autoimmune arthritis;Autoimmune blistering disease;Autoimmune cholangitis;Autoimmune colitis;Autoimmune demyelinating disease;Autoimmune dermatitis;Autoimmune disorder;Autoimmune encephalopathy;Autoimmune endocrine disorder;Autoimmune enteropathy;Autoimmune eye disorder;Autoimmune haemolytic anaemia;Autoimmune heparin-induced thrombocytopenia;Autoimmune hepatitis;Autoimmune hyperlipidaemia;Autoimmune hypothyroidism;Autoimmune inner ear disease;Autoimmune lung disease;Autoimmune lymphoproliferative syndrome;Autoimmune myocarditis;Autoimmune myositis;Autoimmune nephritis;Autoimmune neuropathy;Autoimmune neutropenia;Autoimmune pancreatitis;Autoimmune pancytopenia;Autoimmune pericarditis;Autoimmune retinopathy;Autoimmune thyroid disorder;Autoimmune thyroiditis;Autoimmune uveitis;Autoinflammation with infantile enterocolitis;Autoinflammatory disease;Automatism epileptic;Autonomic nervous system imbalance;Autonomic seizure;Axial spondyloarthritis;Axillary vein thrombosis;Axonal and demyelinating polyneuropathy;Axonal neuropathy;Bacterascites;Baltic myoclonic epilepsy;Band sensation;Basedow's disease;Basilar artery thrombosis;Basophilopenia;B-cell aplasia;Behcet's syndrome;Benign ethnic neutropenia;Benign familial neonatal convulsions;Benign familial pemphigus;Benign rolandic epilepsy;Beta-2 glycoprotein antibody positive;Bickerstaff's encephalitis;Bile output abnormal;Bile output decreased;Biliary ascites;Bilirubin conjugated abnormal;Bilirubin conjugated increased;Bilirubin urine present;Biopsy liver abnormal;Biotinidase deficiency;Birdshot chorioretinopathy;Blood alkaline phosphatase abnormal;Blood alkaline phosphatase increased;Blood bilirubin abnormal;Blood bilirubin increased;Blood bilirubin unconjugated increased;Blood cholinesterase abnormal;Blood cholinesterase decreased;Blood pressure decreased;Blood pressure diastolic decreased;Blood pressure systolic decreased;Blue toe syndrome;Brachiocephalic vein thrombosis;Brain stem embolism;Brain stem thrombosis;Bromosulphthalein test abnormal;Bronchial oedema;Bronchitis;Bronchitis mycoplasmal;Bronchitis viral;Bronchopulmonary aspergillosis allergic;Bronchospasm;Budd-Chiari syndrome;Bulbar palsy;Butterfly rash;C1q nephropathy;Caesarean section;Calcium embolism;Capillaritis;Caplan's syndrome;Cardiac amyloidosis;Cardiac arrest;Cardiac failure;Cardiac failure acute;Cardiac sarcoidosis;Cardiac ventricular thrombosis;Cardiogenic shock;Cardiolipin antibody positive;Cardiopulmonary failure;Cardio-respiratory arrest;Cardio-respiratory distress;Cardiovascular insufficiency;Carotid arterial embolus;Carotid artery thrombosis;Cataplexy;Catheter site thrombosis;Catheter site vasculitis;Cavernous sinus thrombosis;CDKL5 deficiency disorder;CEC syndrome;Cement embolism;Central nervous system lupus;Central nervous system vasculitis;Cerebellar artery thrombosis;Cerebellar embolism;Cerebral amyloid angiopathy;Cerebral arteritis;Cerebral artery embolism;Cerebral artery thrombosis;Cerebral gas embolism;Cerebral microembolism;Cerebral septic infarct;Cerebral thrombosis;Cerebral venous sinus thrombosis;Cerebral venous thrombosis;Cerebrospinal thrombotic

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tamponade;Cerebrovascular accident;Change in seizure presentation;Chest discomfort;Child-Pugh-Turcotte score abnormal;Child-Pugh-Turcotte score increased;Chillblains;Choking;Choking sensation;Cholangitis sclerosing;Chronic autoimmune glomerulonephritis;Chronic cutaneous lupus erythematosus;Chronic fatigue syndrome;Chronic gastritis;Chronic inflammatory demyelinating polyradiculoneuropathy;Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids;Chronic recurrent multifocal osteomyelitis;Chronic respiratory failure;Chronic spontaneous urticaria;Circulatory collapse;Circumoral oedema;Circumoral swelling;Clinically isolated syndrome;Clonic convulsion;Coeliac disease;Cogan's syndrome;Cold agglutinins positive;Cold type haemolytic anaemia;Colitis;Colitis erosive;Colitis herpes;Colitis microscopic;Colitis ulcerative;Collagen disorder;Collagen-vascular disease;Complement factor abnormal;Complement factor C1 decreased;Complement factor C2 decreased;Complement factor C3 decreased;Complement factor C4 decreased;Complement factor decreased;Computerised tomogram liver abnormal;Concentric sclerosis;Congenital anomaly;Congenital bilateral perisylvian syndrome;Congenital herpes simplex infection;Congenital myasthenic syndrome;Congenital varicella infection;Congestive hepatopathy;Convulsion in childhood;Convulsions local;Convulsive threshold lowered;Coombs positive haemolytic anaemia;Coronary artery disease;Coronary artery embolism;Coronary artery thrombosis;Coronary bypass thrombosis;Coronavirus infection;Coronavirus test;Coronavirus test negative;Coronavirus test positive;Corpus callosotomy;Cough;Cough variant asthma;COVID-19;COVID-19 immunisation;COVID-19 pneumonia;COVID-19 prophylaxis;COVID-19 treatment;Cranial nerve disorder;Cranial nerve palsies multiple;Cranial nerve paralysis;CREST syndrome;Crohn's disease;Cryofibrinogenaemia;Cryoglobulinaemia;CSF oligoclonal band present;CSWS syndrome;Cutaneous amyloidosis;Cutaneous lupus erythematosus;Cutaneous sarcoidosis;Cutaneous vasculitis;Cyanosis;Cyclic neutropenia;Cystitis interstitial;Cytokine release syndrome;Cytokine storm;De novo purine synthesis inhibitors associated acute inflammatory syndrome;Death neonatal;Deep vein thrombosis;Deep vein thrombosis postoperative;Deficiency of bile secretion;Deja vu;Demyelinating polyneuropathy;Demyelination;Dermatitis;Dermatitis bullous;Dermatitis herpetiformis;Dermatomyositis;Device embolisation;Device related thrombosis;Diabetes mellitus;Diabetic ketoacidosis;Diabetic mastopathy;Dialysis amyloidosis;Dialysis membrane reaction;Diastolic hypotension;Diffuse vasculitis;Digital pitting scar;Disseminated intravascular coagulation;Disseminated intravascular coagulation in newborn;Disseminated neonatal herpes simplex;Disseminated varicella;Disseminated varicella zoster vaccine virus infection;Disseminated varicella zoster virus infection;DNA antibody positive;Double cortex syndrome;Double stranded DNA antibody positive;Dreamy state;Dressler's syndrome;Drop attacks;Drug withdrawal convulsions;Dyspnoea;Early infantile epileptic encephalopathy with burst-suppression;Eclampsia;Eczema herpeticum;Embolia cutis medicamentosa;Embolic cerebellar infarction;Embolic cerebral infarction;Embolic pneumonia;Embolic stroke;Embolism;Embolism arterial;Embolism venous;Encephalitis;Encephalitis allergic;Encephalitis autoimmune;Encephalitis brain stem;Encephalitis haemorrhagic;Encephalitis periaxialis diffusa;Encephalitis post immunisation;Encephalomyelitis;Encephalopathy;Endocrine disorder;Endocrine ophthalmopathy;Endotracheal intubation;Enteritis;Enteritis leukopenic;Enterobacter pneumonia;Enterocolitis;Enteropathic spondylitis;Eosinopenia;Eosinophilic

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fasciitis;Eosinophilic granulomatosis with polyangiitis;Eosinophilic oesophagitis;Epidermolysis;Epilepsy;Epilepsy surgery;Epilepsy with myoclonic-atonic seizures;Epileptic aura;Epileptic psychosis;Erythema;Erythema induratum;Erythema multiforme;Erythema nodosum;Evans syndrome;Exanthema subitum;Expanded disability status scale score decreased;Expanded disability status scale score increased;Exposure to communicable disease;Exposure to SARS-CoV-2;Eye oedema;Eye pruritus;Eye swelling;Eyelid oedema;Face oedema;Facial paralysis;Facial paresis;Faciobrachial dystonic seizure;Fat embolism;Febrile convulsion;Febrile infection-related epilepsy syndrome;Febrile neutropenia;Felty's syndrome;Femoral artery embolism;Fibrillary glomerulonephritis;Fibromyalgia;Flushing;Foaming at mouth;Focal cortical resection;Focal dyscognitive seizures;Foetal distress syndrome;Foetal placental thrombosis;Foetor hepaticus;Foreign body embolism;Frontal lobe epilepsy;Fulminant type 1 diabetes mellitus;Galactose elimination capacity test abnormal;Galactose elimination capacity test decreased;Gamma-glutamyltransferase abnormal;Gamma-glutamyltransferase increased;Gastritis herpes;Gastrointestinal amyloidosis;Gelastic seizure;Generalised onset non-motor seizure;Generalised tonic-clonic seizure;Genital herpes;Genital herpes simplex;Genital herpes zoster;Giant cell arteritis;Glomerulonephritis;Glomerulonephritis membranoproliferative;Glomerulonephritis membranous;Glomerulonephritis rapidly progressive;Glossopharyngeal nerve paralysis;Glucose transporter type 1 deficiency syndrome;Glutamate dehydrogenase increased;Glycocholic acid increased;GM2 gangliosidosis;Goodpasture's syndrome;Graft thrombosis;Granulocytopenia;Granulocytopenia neonatal;Granulomatosis with polyangiitis;Granulomatous dermatitis;Grey matter heterotopia;Guanase increased;Guillain-Barre syndrome;Haemolytic anaemia;Haemophagocytic lymphohistiocytosis;Haemorrhage;Haemorrhagic ascites;Haemorrhagic disorder;Haemorrhagic pneumonia;Haemorrhagic varicella syndrome;Haemorrhagic vasculitis;Hantavirus pulmonary infection;Hashimoto's encephalopathy;Hashitoxicosis;Hemimegalencephaly;Henoch-Schonlein purpura;Henoch-Schonlein purpura nephritis;Hepaplastin abnormal;Hepaplastin decreased;Heparin-induced thrombocytopenia;Hepatic amyloidosis;Hepatic artery embolism;Hepatic artery flow decreased;Hepatic artery thrombosis;Hepatic enzyme abnormal;Hepatic enzyme decreased;Hepatic enzyme increased;Hepatic fibrosis marker abnormal;Hepatic fibrosis marker increased;Hepatic function abnormal;Hepatic hydrothorax;Hepatic hypertrophy;Hepatic hypoperfusion;Hepatic lymphocytic infiltration;Hepatic mass;Hepatic pain;Hepatic sequestration;Hepatic vascular resistance increased;Hepatic vascular thrombosis;Hepatic vein embolism;Hepatic vein thrombosis;Hepatic venous pressure gradient abnormal;Hepatic venous pressure gradient increased;Hepatitis;Hepatobiliary scan abnormal;Hepatomegaly;Hepatosplenomegaly;Hereditary angioedema with C1 esterase inhibitor deficiency;Herpes dermatitis;Herpes gestationis;Herpes oesophagitis;Herpes ophthalmic;Herpes pharyngitis;Herpes sepsis;Herpes simplex;Herpes simplex cervicitis;Herpes simplex colitis;Herpes simplex encephalitis;Herpes simplex gastritis;Herpes simplex hepatitis;Herpes simplex meningitis;Herpes simplex meningoencephalitis;Herpes simplex meningomyelitis;Herpes simplex necrotising retinopathy;Herpes simplex oesophagitis;Herpes simplex otitis externa;Herpes simplex pharyngitis;Herpes simplex pneumonia;Herpes simplex reactivation;Herpes simplex sepsis;Herpes simplex viraemia;Herpes simplex virus conjunctivitis neonatal;Herpes simplex visceral;Herpes virus

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infection;Herpes zoster;Herpes zoster cutaneous disseminated;Herpes zoster infection neurological;Herpes zoster meningitis;Herpes zoster meningoencephalitis;Herpes zoster meningomyelitis;Herpes zoster meningoradiculitis;Herpes zoster necrotising retinopathy;Herpes zoster oticus;Herpes zoster pharyngitis;Herpes zoster reactivation;Herpetic radiculopathy;Histone antibody positive;Hoigne's syndrome;Human herpesvirus 6 encephalitis;Human herpesvirus 6 infection;Human herpesvirus 6 infection reactivation;Human herpesvirus 7 infection;Human herpesvirus 8 infection;Hyperammonaemia;Hyperbilirubinaemia;Hypercholia;Hypergammaglobulinaemia benign monoclonal;Hyperglycaemic seizure;Hypersensitivity;Hypersensitivity vasculitis;Hyperthyroidism;Hypertransaminasaemia;Hyperventilation;Hypoalbuminaemia;Hypocalcaemic seizure;Hypogammaglobulinaemia;Hypoglossal nerve paralysis;Hypoglossal nerve paresis;Hypoglycaemic seizure;Hyponatraemic seizure;Hypotension;Hypotensive crisis;Hypothenar hammer syndrome;Hypothyroidism;Hypoxia;Idiopathic CD4 lymphocytopenia;Idiopathic generalised epilepsy;Idiopathic interstitial pneumonia;Idiopathic neutropenia;Idiopathic pulmonary fibrosis;IgA nephropathy;IgM nephropathy;IIIrd nerve paralysis;IIIrd nerve paresis;Iliac artery embolism;Immune thrombocytopenia;Immune-mediated adverse reaction;Immune-mediated cholangitis;Immune-mediated cholestasis;Immune-mediated cytopenia;Immune-mediated encephalitis;Immune-mediated encephalopathy;Immune-mediated endocrinopathy;Immune-mediated enterocolitis;Immune-mediated gastritis;Immune-mediated hepatic disorder;Immune-mediated hepatitis;Immune-mediated hyperthyroidism;Immune-mediated hypothyroidism;Immune-mediated myocarditis;Immune-mediated myositis;Immune-mediated nephritis;Immune-mediated neuropathy;Immune-mediated pancreatitis;Immune-mediated pneumonitis;Immune-mediated renal disorder;Immune-mediated thyroiditis;Immune-mediated uveitis;Immunoglobulin G4 related disease;Immunoglobulins abnormal;Implant site thrombosis;Inclusion body myositis;Infantile genetic agranulocytosis;Infantile spasms;Infected vasculitis;Infective thrombosis;Inflammation;Inflammatory bowel disease;Infusion site thrombosis;Infusion site vasculitis;Injection site thrombosis;Injection site urticaria;Injection site vasculitis;Instillation site thrombosis;Insulin autoimmune syndrome;Interstitial granulomatous dermatitis;Interstitial lung disease;Intracardiac mass;Intracardiac thrombus;Intracranial pressure increased;Intrapericardial thrombosis;Intrinsic factor antibody abnormal;Intrinsic factor antibody positive;IPEX syndrome;Irregular breathing;IRVAN syndrome;IVth nerve paralysis;IVth nerve paresis;JC polyomavirus test positive;JC virus CSF test positive;Jeavons syndrome;Jugular vein embolism;Jugular vein thrombosis;Juvenile idiopathic arthritis;Juvenile myoclonic epilepsy;Juvenile polymyositis;Juvenile psoriatic arthritis;Juvenile spondyloarthritis;Kaposi sarcoma inflammatory cytokine syndrome;Kawasaki's disease;Kayser-Fleischer ring;Keratoderma blenorrhagica;Ketosis-prone diabetes mellitus;Kounis syndrome;Lafora's myoclonic epilepsy;Lambl's excrescences;Laryngeal dyspnoea;Laryngeal oedema;Laryngeal rheumatoid arthritis;Laryngospasm;Laryngotracheal oedema;Latent autoimmune diabetes in adults;LE cells present;Lemierre syndrome;Lennox-Gastaut syndrome;Leucine aminopeptidase increased;Leukoencephalomyelitis;Leukoencephalopathy;Leukopenia;Leukopenia neonatal;Lewis-Sumner syndrome;Lhermitte's sign;Lichen planopilaris;Lichen planus;Lichen sclerosus;Limbic encephalitis;Linear IgA disease;Lip oedema;Lip swelling;Liver function test abnormal;Liver function test decreased;Liver function test increased;Liver induration;Liver injury;Liver iron concentration abnormal;Liver iron concentration

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increased;Liver opacity;Liver palpable;Liver sarcoidosis;Liver scan abnormal;Liver tenderness;Low birth weight baby;Lower respiratory tract herpes infection;Lower respiratory tract infection;Lower respiratory tract infection viral;Lung abscess;Lupoid hepatic cirrhosis;Lupus cystitis;Lupus encephalitis;Lupus endocarditis;Lupus enteritis;Lupus hepatitis;Lupus myocarditis;Lupus myositis;Lupus nephritis;Lupus pancreatitis;Lupus pleurisy;Lupus pneumonitis;Lupus vasculitis;Lupus-like syndrome;Lymphocytic hypophysitis;Lymphocytopenia neonatal;Lymphopenia;MAGIC syndrome;Magnetic resonance imaging liver abnormal;Magnetic resonance proton density fat fraction measurement;Mahler sign;Manufacturing laboratory analytical testing issue;Manufacturing materials issue;Manufacturing production issue;Marburg's variant multiple sclerosis;Marchiafava-Bignami disease;Marine Lenhart syndrome;Mastocytic enterocolitis;Maternal exposure during pregnancy;Medical device site thrombosis;Medical device site vasculitis;MELAS syndrome;Meningitis;Meningitis aseptic;Meningitis herpes;Meningoencephalitis herpes simplex neonatal;Meningoencephalitis herpetic;Meningomyelitis herpes;MERS-CoV test;MERS-CoV test negative;MERS-CoV test positive;Mesangioproliferative glomerulonephritis;Mesenteric artery embolism;Mesenteric artery thrombosis;Mesenteric vein thrombosis;Metapneumovirus infection;Metastatic cutaneous Crohn's disease;Metastatic pulmonary embolism;Microangiopathy;Microembolism;Microscopic polyangiitis;Middle East respiratory syndrome;Migraine-triggered seizure;Miliary pneumonia;Miller Fisher syndrome;Mitochondrial aspartate aminotransferase increased;Mixed connective tissue disease;Model for end stage liver disease score abnormal;Model for end stage liver disease score increased;Molar ratio of total branched-chain amino acid to tyrosine;Molybdenum cofactor deficiency;Monocytopenia;Mononeuritis;Mononeuropathy multiplex;Morphoea;Morvan syndrome;Mouth swelling;Moyamoya disease;Multifocal motor neuropathy;Multiple organ dysfunction syndrome;Multiple sclerosis;Multiple sclerosis relapse;Multiple sclerosis relapse prophylaxis;Multiple subpial transection;Multisystem inflammatory syndrome in children;Muscular sarcoidosis;Myasthenia gravis;Myasthenia gravis crisis;Myasthenia gravis neonatal;Myasthenic syndrome;Myelitis;Myelitis transverse;Myocardial infarction;Myocarditis;Myocarditis post infection;Myoclonic epilepsy;Myoclonic epilepsy and ragged-red fibres;Myokymia;Myositis;Narcolepsy;Nasal herpes;Nasal obstruction;Necrotising herpetic retinopathy;Neonatal Crohn's disease;Neonatal epileptic seizure;Neonatal lupus erythematosus;Neonatal mucocutaneous herpes simplex;Neonatal pneumonia;Neonatal seizure;Nephritis;Nephrogenic systemic fibrosis;Neuralgic amyotrophy;Neuritis;Neuritis cranial;Neuromyelitis optica pseudo relapse;Neuromyelitis optica spectrum disorder;Neuromyotonia;Neuronal neuropathy;Neuropathy peripheral;Neuropathy, ataxia, retinitis pigmentosa syndrome;Neuropsychiatric lupus;Neurosarcoidosis;Neutropenia;Neutropenia neonatal;Neutropenic colitis;Neutropenic infection;Neutropenic sepsis;Nodular rash;Nodular vasculitis;Noninfectious myelitis;Noninfective encephalitis;Noninfective encephalomyelitis;Noninfective oophoritis;Obstetrical pulmonary embolism;Occupational exposure to communicable disease;Occupational exposure to SARS-CoV-2;Ocular hyperaemia;Ocular myasthenia;Ocular pemphigoid;Ocular sarcoidosis;Ocular vasculitis;Oculofacial paralysis;Oedema;Oedema blister;Oedema due to hepatic disease;Oedema mouth;Oesophageal achalasia;Ophthalmic artery thrombosis;Ophthalmic herpes simplex;Ophthalmic herpes zoster;Ophthalmic vein thrombosis;Optic neuritis;Optic

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neuropathy;Optic perineuritis;Oral herpes;Oral lichen planus;Oropharyngeal oedema;Oropharyngeal spasm;Oropharyngeal swelling;Osmotic demyelination syndrome;Ovarian vein thrombosis;Overlap syndrome;Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection;Paget-Schroetter syndrome;Palindromic rheumatism;Palisaded neutrophilic granulomatous dermatitis;Palmoplantar keratoderma;Palpable purpura;Pancreatitis;Panencephalitis;Papillophlebitis;Paracancerous pneumonia;Paradoxical embolism;Parainfluenzae viral laryngotracheobronchitis;Paraneoplastic dermatomyositis;Paraneoplastic pemphigus;Paraneoplastic thrombosis;Paresis cranial nerve;Parietal cell antibody positive;Paroxysmal nocturnal haemoglobinuria;Partial seizures;Partial seizures with secondary generalisation;Patient isolation;Pelvic venous thrombosis;Pemphigoid;Pemphigus;Penile vein thrombosis;Pericarditis;Pericarditis lupus;Perihepatic discomfort;Periorbital oedema;Periorbital swelling;Peripheral artery thrombosis;Peripheral embolism;Peripheral ischaemia;Peripheral vein thrombus extension;Periportal oedema;Peritoneal fluid protein abnormal;Peritoneal fluid protein decreased;Peritoneal fluid protein increased;Peritonitis lupus;Pernicious anaemia;Petit mal epilepsy;Pharyngeal oedema;Pharyngeal swelling;Pityriasis lichenoides et varioliformis acuta;Placenta praevia;Pleuroparenchymal fibroelastosis;Pneumobilia;Pneumonia;Pneumonia adenoviral;Pneumonia cytomegaloviral;Pneumonia herpes viral;Pneumonia influenzal;Pneumonia measles;Pneumonia mycoplasmal;Pneumonia necrotising;Pneumonia parainfluenzae viral;Pneumonia respiratory syncytial viral;Pneumonia viral;POEMS syndrome;Polyarteritis nodosa;Polyarthritis;Polychondritis;Polyglandular autoimmune syndrome type I;Polyglandular autoimmune syndrome type II;Polyglandular autoimmune syndrome type III;Polyglandular disorder;Polymicrogyria;Polymyalgia rheumatica;Polymyositis;Polyneuropathy;Polyneuropathy idiopathic progressive;Portal pyaemia;Portal vein embolism;Portal vein flow decreased;Portal vein pressure increased;Portal vein thrombosis;Portosplenomesenteric venous thrombosis;Post procedural hypotension;Post procedural pneumonia;Post procedural pulmonary embolism;Post stroke epilepsy;Post stroke seizure;Post thrombotic retinopathy;Post thrombotic syndrome;Post viral fatigue syndrome;Postictal headache;Postictal paralysis;Postictal psychosis;Postictal state;Postoperative respiratory distress;Postoperative respiratory failure;Postoperative thrombosis;Postpartum thrombosis;Postpartum venous thrombosis;Postpericardiotomy syndrome;Post-traumatic epilepsy;Postural orthostatic tachycardia syndrome;Precerebral artery thrombosis;Pre-eclampsia;Preictal state;Premature labour;Premature menopause;Primary amyloidosis;Primary biliary cholangitis;Primary progressive multiple sclerosis;Procedural shock;Proctitis herpes;Proctitis ulcerative;Product availability issue;Product distribution issue;Product supply issue;Progressive facial hemiatrophy;Progressive multifocal leukoencephalopathy;Progressive multiple sclerosis;Progressive relapsing multiple sclerosis;Prosthetic cardiac valve thrombosis;Pruritus;Pruritus allergic;Pseudovasculitis;Psoriasis;Psoriatic arthropathy;Pulmonary amyloidosis;Pulmonary artery thrombosis;Pulmonary embolism;Pulmonary fibrosis;Pulmonary haemorrhage;Pulmonary microemboli;Pulmonary oil microembolism;Pulmonary renal syndrome;Pulmonary sarcoidosis;Pulmonary sepsis;Pulmonary thrombosis;Pulmonary tumour thrombotic microangiopathy;Pulmonary vasculitis;Pulmonary veno-occlusive disease;Pulmonary venous thrombosis;Pyoderma gangrenosum;Pyostomatitis vegetans;Pyrexia;Quarantine;Radiation leukopenia;Radiculitis

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brachial;Radiologically isolated syndrome;Rash;Rash erythematous;Rash pruritic;Rasmussen encephalitis;Raynaud's phenomenon;Reactive capillary endothelial proliferation;Relapsing multiple sclerosis;Relapsing-remitting multiple sclerosis;Renal amyloidosis;Renal arteritis;Renal artery thrombosis;Renal embolism;Renal failure;Renal vascular thrombosis;Renal vasculitis;Renal vein embolism;Renal vein thrombosis;Respiratory arrest;Respiratory disorder;Respiratory distress;Respiratory failure;Respiratory paralysis;Respiratory syncytial virus bronchiolitis;Respiratory syncytial virus bronchitis;Retinal artery embolism;Retinal artery occlusion;Retinal artery thrombosis;Retinal vascular thrombosis;Retinal vasculitis;Retinal vein occlusion;Retinal vein thrombosis;Retinol binding protein decreased;Retinopathy;Retrograde portal vein flow;Retroperitoneal fibrosis;Reversible airways obstruction;Reynold's syndrome;Rheumatic brain disease;Rheumatic disorder;Rheumatoid arthritis;Rheumatoid factor increased;Rheumatoid factor positive;Rheumatoid factor quantitative increased;Rheumatoid lung;Rheumatoid neutrophilic dermatosis;Rheumatoid nodule;Rheumatoid nodule removal;Rheumatoid scleritis;Rheumatoid vasculitis;Saccadic eye movement;SAPHO syndrome;Sarcoidosis;SARS-CoV-1 test;SARS-CoV-1 test negative;SARS-CoV-1 test positive;SARS-CoV-2 antibody test;SARS-CoV-2 antibody test negative;SARS-CoV-2 antibody test positive;SARS-CoV-2 carrier;SARS-CoV-2 sepsis;SARS-CoV-2 test;SARS-CoV-2 test false negative;SARS-CoV-2 test false positive;SARS-CoV-2 test negative;SARS-CoV-2 test positive;SARS-CoV-2 viraemia;Satoyoshi syndrome;Schizencephaly;Scleritis;Sclerodactylia;Scleroderma;Scleroderma associated digital ulcer;Scleroderma renal crisis;Scleroderma-like reaction;Secondary amyloidosis;Secondary cerebellar degeneration;Secondary progressive multiple sclerosis;Segmented hyalinising vasculitis;Seizure;Seizure anoxic;Seizure cluster;Seizure like phenomena;Seizure prophylaxis;Sensation of foreign body;Septic embolus;Septic pulmonary embolism;Severe acute respiratory syndrome;Severe myoclonic epilepsy of infancy;Shock;Shock symptom;Shrinking lung syndrome;Shunt thrombosis;Silent thyroiditis;Simple partial seizures;Sjogren's syndrome;Skin swelling;SLE arthritis;Smooth muscle antibody positive;Sneezing;Spinal artery embolism;Spinal artery thrombosis;Splenic artery thrombosis;Splenic embolism;Splenic thrombosis;Splenic vein thrombosis;Spondylitis;Spondyloarthropathy;Spontaneous heparin-induced thrombocytopenia syndrome;Status epilepticus;Stevens-Johnson syndrome;Stiff leg syndrome;Stiff person syndrome;Stillbirth;Still's disease;Stoma site thrombosis;Stoma site vasculitis;Stress cardiomyopathy;Stridor;Subacute cutaneous lupus erythematosus;Subacute endocarditis;Subacute inflammatory demyelinating polyneuropathy;Subclavian artery embolism;Subclavian artery thrombosis;Subclavian vein thrombosis;Sudden unexplained death in epilepsy;Superior sagittal sinus thrombosis;Susac's syndrome;Suspected COVID-19;Swelling;Swelling face;Swelling of eyelid;Swollen tongue;Sympathetic ophthalmia;Systemic lupus erythematosus;Systemic lupus erythematosus disease activity index abnormal;Systemic lupus erythematosus disease activity index decreased;Systemic lupus erythematosus disease activity index increased;Systemic lupus erythematosus rash;Systemic scleroderma;Systemic sclerosis pulmonary;Tachycardia;Tachypnoea;Takayasu's arteritis;Temporal lobe epilepsy;Terminal ileitis;Testicular autoimmunity;Throat tightness;Thromboangiitis obliterans;Thrombocytopenia;Thrombocytopenic purpura;Thrombophlebitis;Thrombophlebitis migrans;Thrombophlebitis

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neonatal;Thrombophlebitis septic;Thrombophlebitis superficial;Thromboplastin antibody positive;Thrombosis;Thrombosis corpora cavernosa;Thrombosis in device;Thrombosis mesenteric vessel;Thrombotic cerebral infarction;Thrombotic microangiopathy;Thrombotic stroke;Thrombotic thrombocytopenic purpura;Thyroid disorder;Thyroid stimulating immunoglobulin increased;Thyroiditis;Tongue amyloidosis;Tongue biting;Tongue oedema;Tonic clonic movements;Tonic convulsion;Tonic posturing;Topectomy;Total bile acids increased;Toxic epidermal necrolysis;Toxic leukoencephalopathy;Toxic oil syndrome;Tracheal obstruction;Tracheal oedema;Tracheobronchitis;Tracheobronchitis mycoplasmal;Tracheobronchitis viral;Transaminases abnormal;Transaminases increased;Transfusion-related alloimmune neutropenia;Transient epileptic amnesia;Transverse sinus thrombosis;Trigeminal nerve paresis;Trigeminal neuralgia;Trigeminal palsy;Truncus coeliacus thrombosis;Tuberous sclerosis complex;Tubulointerstitial nephritis and uveitis syndrome;Tumefactive multiple sclerosis;Tumour embolism;Tumour thrombosis;Type 1 diabetes mellitus;Type I hypersensitivity;Type III immune complex mediated reaction;Uhthoff's phenomenon;Ulcerative keratitis;Ultrasound liver abnormal;Umbilical cord thrombosis;Uncinate fits;Undifferentiated connective tissue disease;Upper airway obstruction;Urine bilirubin increased;Urobilinogen urine decreased;Urobilinogen urine increased;Urticaria;Urticaria papular;Urticarial vasculitis;Uterine rupture;Uveitis;Vaccination site thrombosis;Vaccination site vasculitis;Vagus nerve paralysis;Varicella;Varicella keratitis;Varicella post vaccine;Varicella zoster gastritis;Varicella zoster oesophagitis;Varicella zoster pneumonia;Varicella zoster sepsis;Varicella zoster virus infection;Vasa praevia;Vascular graft thrombosis;Vascular pseudoaneurysm thrombosis;Vascular purpura;Vascular stent thrombosis;Vasculitic rash;Vasculitic ulcer;Vasculitis;Vasculitis gastrointestinal;Vasculitis necrotising;Vena cava embolism;Vena cava thrombosis;Venous intravasation;Venous recanalisation;Venous thrombosis;Venous thrombosis in pregnancy;Venous thrombosis limb;Venous thrombosis neonatal;Vertebral artery thrombosis;Vessel puncture site thrombosis;Visceral venous thrombosis;VIth nerve paralysis;VIth nerve paresis;Vitiligo;Vocal cord paralysis;Vocal cord paresis;Vogt-Koyanagi-Harada disease;Warm type haemolytic anaemia;Wheezing;White nipple sign;XIth nerve paralysis;X-ray hepatobiliary abnormal;Young's syndrome;Zika virus associated Guillain Barre syndrome.

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Grant Final Report

Grant ID: R18 HS 017045

Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP:VAERS)

Inclusive dates: 12/01/07 - 09/30/10

Principal Investigator:
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Submitted to:
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Abstract

Purpose: To develop and disseminate HIT evidence and evidence-based tools to improve healthcare decision making through the use of integrated data and knowledge management.

Scope: To create a generalizable system to facilitate detection and clinician reporting of vaccine adverse events, in order to improve the safety of national vaccination programs.

Methods: Electronic medical records available from all ambulatory care encounters in a large multi-specialty practice were used. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions were evaluated for values suggestive of an adverse event.

Results: Restructuring at CDC and consequent delays in terms of decision making have made it challenging despite best efforts to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial and comparison of ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. However, Preliminary data were collected and analyzed and this initiative has been presented at a number of national symposia.

Key Words: electronic health records, vaccinations, adverse event reporting

The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.

Final Report

Purpose

This research project was funded to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS), via the following aims:

Aim 1. Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration.

Aim 2. Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS).

Aim 3. Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.

Aim 4. Distribute documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems.

Scope

Public and professional confidence in vaccination depends on reliable postmarketing surveillance systems to ensure that rare and unexpected adverse effects are rapidly identified. The goal of this project is to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS). This project is serving as an extension of the Electronic Support for Public Health (ESP) project, an automated system using electronic health record (EHR) data to detect and securely report cases of certain diseases to a local public health authority. ESP provides a ready-made platform for automatically converting clinical, laboratory, prescription, and demographic data from almost any EHR system into database tables on a completely independent server, physically located and secured by the same logical and physical security as the EHR data itself. The ESP:VAERS project developed criteria and algorithms to identify important adverse events related to vaccinations in ambulatory care EHR data, and made attempts at formatting and securely sending electronic VAERS reports directly to the Centers for Disease Control and Prevention (CDC).

Patient data were available from Epic System's Certification Commission for Health Information Technology-certified EpicCare system at all ambulatory care encounters within Atrius Health, a large multispecialty group practice with over 35 facilities. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions are evaluated for values

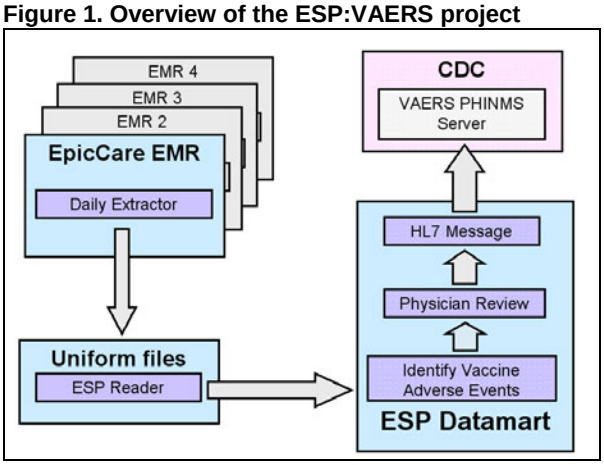
suggestive of an adverse vaccine event. When a possible adverse event was detected, it was recorded, and the appropriate clinician was to be notified electronically.

Clinicians in-basket messaging was designed to provide a preview a pre-populated report with information from the EHR about the patient, including vaccine type, lot number, and possible adverse effect, to inform their clinical judgment regarding whether they wish to send a report to VAERS. Clinicians would then have the option of adding free-text comments to pre-populated VAERS reports or to document their decision not to send a report. The CDC's Public Health Information Network Messaging System (PHIN-MS) software was installed within the facilities so that the approved reports could be securely transferred to VAERS as electronic messages in an interoperable health data exchange format using Health Level 7 (HL7).

Methods

The goal of Aim 1: *Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration,* and Aim 2: *Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS),* was to construct the below flow of data in order to support the first two Aims:

Figure 1. Overview of the ESP:VAERS project



Existing and functioning ESP components are shown on the left, and Aims 1 and 2 on the right. ESP:VAERS flags every vaccinated patient, and prospectively accumulate that patient's diagnostic codes, laboratory tests, allergy lists, vital signs, and medication prescriptions. A main component of Aim 1 was to *Develop AE criteria to assess these parameters for new or abnormal values that might be suggestive of an adverse effect.* A reporting protocol & corresponding algorithms were developed to detect potential adverse event cases using diagnostic codes, and methods were tested to identify prescriptions or abnormal laboratory values that might be suggestive of an adverse effect. These algorithms were designed to seek both expected and unexpected adverse effects.

This reporting protocol was approved by both internal & external partners. We initially prepared a draft document describing the elements, algorithms, interval of interest after vaccination, and actions for broad classes of post-vaccination events, including those to be reported immediately without delay (such as acute anaphylactic reaction following vaccination), those never to be reported (such as routine check-ups following vaccination) and those to be reported at the discretion and with additional information from the attending physician through a feedback mechanism. The draft was then widely circulated as an initial / working draft for comment by relevant staff in the CDC and among our clinical colleagues at Atrius. In addition to review by the internal CDC Brighton Collaboration liaison, this protocol has also received review & comment via the CDC's Clinical Immunization Safety Assessment (CISA) Network.

The goal of Aim 2 was the *Development of HL7 messages code for ESP:VAERS to ensure secure transmission to CDC via PHIN-MS*. The HL7 specification describing the elements for an electronic message to be submitted to Constella, the consultants engaged by CDC for this project was implemented. Synthetic and real test data was been generated and transmitted between Harvard and Constella. However, real data transmissions of non-physician approved reports to the CDC was unable to commence, as by the end of this project, the CDC had yet to respond to multiple requests to partner for this activity.

The goal of Aim 3 was to *Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.*

We had initially planned to evaluate the system by comparing adverse event findings to those in the Vaccine Safety Datalink project—a collaborative effort between CDC's Immunization Safety Office and eight large managed care organizations. Through a randomized trial, we would also test the hypothesis that the combination of secure, computer-assisted, clinician-approved, adverse event detection, and automated electronic reporting will substantially increase the number, completeness, validity, and timeliness of physician-approved case reports to VAERS compared to the existing spontaneous reporting system; however, due to restructuring at CDC and consequent delays in terms of decision making, it became impossible to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial, and compare ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. Therefore, the components under this particular Aim were not achieved.

Aim 4 *Distribution of documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems* has been successfully completed. Functioning source code is available to share under an approved open source license. ESP:VAERS source code is available as part of the ESP source code distribution. It is licensed under the LGPL, an open source license compatible with commercial use. We have added the ESP:VAERS code, HL7 and other specifications and documentation to the existing ESP web documentation and distribution resource center http://esphealth.org, specifically, the Subversion repository available at:
http://esphealth.org/trac/ESP/wiki/ESPVAERS.

Results

Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions (2.6 percent of vaccinations) were identified. This is an average of 890 possible events, an average of 1.3 events per clinician, per month. These data were presented at the 2009 AMIA conference.

In addition, ESP:VAERS investigators participated on a panel to explore the perspective of clinicians, electronic health record (EHR) vendors, the pharmaceutical industry, and the FDA towards systems that use proactive, automated adverse event reporting.

Adverse events from drugs and vaccines are common, but underreported. Although 25% of ambulatory patients experience an adverse drug event, less than 0.3% of all adverse drug events and 1-13% of serious events are reported to the Food and Drug Administration (FDA). Likewise, fewer than 1% of vaccine adverse events are reported. Low reporting rates preclude or slow the identification of "problem" drugs and vaccines that endanger public health. New surveillance methods for drug and vaccine adverse effects are needed. Barriers to reporting include a lack of clinician awareness, uncertainty about when and what to report, as well as the burdens of reporting: reporting is not part of clinicians' usual workflow, takes time, and is duplicative. Proactive, spontaneous, automated adverse event reporting imbedded within EHRs and other information systems has the potential to speed the identification of problems with new drugs and more careful quantification of the risks of older drugs.

Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed with testing and evaluation.

Inclusion of AHRQ Priority Populations

The focus of our project was the Atrius Health (formerly HealthOne) provider & patient community. This community serves several AHRQ inclusion populations, specifically low-income and minority populations in primarily urban settings.

Atruis currently employs approximately 700 physicians to serve 500,000 patients at more than 18 office sites spread throughout the greater Metropolitan Boston area. The majority of Atruis physicians are primary care internal medicine physicians or pediatricians but the network also includes physicians from every major specialty.

The entire adult and pediatric population served by Atruis was included in our adverse event surveillance system (ESP:VAERS). Atruis serves a full spectrum of patients that reflects the broad diversity of Eastern Massachusetts. A recent analysis suggests that the population served by Atruis is 56% female, 16.6% African American, 4% Hispanic. The prevalence of type 2 diabetes in the adult population is 5.7%. About a quarter of the Atruis population is under age 18.

List of Publications and Products

ESP:VAERS [source code available as part of the ESP source code distribution]. Licensed under the GNU Lesser General Public License (LGPL), an open source license compatible with commercial use. Freely available under an approved open source license at: http://esphealth.org.

Lazarus, R, Klompas M, Hou X, Campion FX, Dunn J, Platt R. Automated Electronic Detection & Reporting of Adverse Events Following Vaccination: ESP:VAERS. The CDC Vaccine Safety Datalink (VSD) Annual Meeting. Atlanta, GA; April, 2008.

Lazarus R, Klompas M Automated vaccine adverse event detection and reporting from electronic medical records. CDC Public Health Informatics Network (PHIN) Conference August 27, 2008.

Klompas M, Lazarus R ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 17th.

Lazarus R, Klompas M, Kruskal B, Platt R Temporal patterns of fever following immunization in ambulatory care data identified by ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

Linder J, Klompas M, Cass B, et al. Spontaneous Electronic Adverse Event Reporting: Perspectives from Clinicians, EHR Vendors, Biopharma, and the FDA. Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

Australian Government
Department of Health

New item for cardiac magnetic resonance imaging (MRI) for myocarditis associated with mRNA COVID-19 vaccination - factsheet

Last updated: 16 December 2021

What are the changes?

From 1 January 2022, Medicare Benefits Schedule (MBS) item 63399 is being introduced for cardiac magnetic resonance imaging (MRI) to assist in diagnosing myocarditis that may occur after vaccination with the mRNA COVID-19 vaccines Comirnaty (Pfizer) and Spikevax (Moderna).

The item is for use in circumstances where myocarditis cannot be definitively diagnosed using conventional imaging and other diagnostic tests.

This is a temporary item. It is being made available pending a full health technology assessment by the Medical Services Advisory Committee (MSAC) on the use of cardiac MRI in diagnosing myocarditis more broadly.

Item 63399 will be available for use from 1 January 2022 to 30 June 2022.

Service/Descriptor

MRI–scan of cardiovascular system for the assessment of myocardial structure and function, if the service is requested by a consultant physician who has assessed the patient, and the request for the scan indicates:

(a) the patient has suspected myocarditis after receiving a mRNA COVID-19 vaccine; and

(b) the patient had symptom onset within 21 days of a mRNA COVID-19 vaccine administration; and

(c) the results from the following examinations are inconclusive to form a diagnosis of myocarditis:

- (i) echocardiogram; and
- (ii) troponin; and
- (iii) chest X-ray.

Applicable not more than once in a patient's lifetime (R) (Anaes.) (Contrast)

Schedule fee: $855.20

Benefit:

85% = $767.30 **75%** = $ 641.40

Why are the changes being made?

Accurate diagnosis of mRNA COVID-19 vaccine associated myocarditis is critical to the ongoing management of Australia's COVID-19 vaccination program, including the rollout of mRNA booster doses, and the extension of mRNA vaccinations to children under the age of 12 years.

What does this mean for requestors?

Consultant physicians can request item 63399 in circumstances where it is clinically necessary, and the request meets the requirements in the item descriptor.

What does this mean for providers?

The cardiac MRI can be provided by a person who is:

(a) a specialist in diagnostic radiology and satisfies the Chief Executive Medicare that the specialist is a participant in the Royal Australian and New Zealand College of Radiologists' Quality and Accreditation Program; or

(b) a specialist in diagnostic radiology or a consultant physician and is recognised by the Conjoint Committee for Certification in Cardiac MRI.

How will these changes affect patients?

Patients who have been vaccinated with Comirnaty (Pfizer) or Spikevax (Moderna) will have access to cardiac MRI in circumstances where it is clinically appropriate.

The item can be used once in a patient's lifetime.

Where can I find more information?

The full item descriptor and explanatory note can be found on the MBS Online website at www.mbsonline.gov.au. You can also subscribe to future MBS updates by visiting MBS Online and clicking 'Subscribe'.

Please note that the information provided is a general guide only. It is ultimately the responsibility of treating practitioners to use their professional judgment to determine the most clinically appropriate services to provide, and then to ensure that any services billed to Medicare fully meet the eligibility requirements outlined in the legislation.

This sheet is current as of the Last updated date shown above and does not account for MBS changes since that date.

Syllabus

NOTE: Where it is feasible, a syllabus (headnote) will be released, as is being done in connection with this case, at the time the opinion is issued. The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States* v. *Detroit Timber & Lumber Co.,* 200 U. S. 321, 337.

SUPREME COURT OF THE UNITED STATES

Syllabus

ASSOCIATION FOR MOLECULAR PATHOLOGY ET AL. *v.* MYRIAD GENETICS, INC., ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

No. 12–398. Argued April 15, 2013—Decided June 13, 2013

Each human gene is encoded as deoxyribonucleic acid (DNA), which takes the shape of a "double helix." Each "cross-bar" in that helix consists of two chemically joined nucleotides. Sequences of DNA nucleotides contain the information necessary to create strings of amino acids used to build proteins in the body. The nucleotides that code for amino acids are "exons," and those that do not are "introns." Scientists can extract DNA from cells to isolate specific segments for study. They can also synthetically create exons-only strands of nucleotides known as complementary DNA (cDNA). cDNA contains only the exons that occur in DNA, omitting the intervening introns.

Respondent Myriad Genetics, Inc. (Myriad), obtained several patents after discovering the precise location and sequence of the BRCA1 and BRCA2 genes, mutations of which can dramatically increase the risk of breast and ovarian cancer. This knowledge allowed Myriad to determine the genes' typical nucleotide sequence, which, in turn, enabled it to develop medical tests useful for detecting mutations in these genes in a particular patient to assess the patient's cancer risk. If valid, Myriad's patents would give it the exclusive right to isolate an individual's BRCA1 and BRCA2 genes, and would give Myriad the exclusive right to synthetically create BRCA cDNA. Petitioners filed suit, seeking a declaration that Myriad's patents are invalid under 35 U. S. C. §101. As relevant here, the District Court granted summary judgment to petitioners, concluding that Myriad's claims were invalid because they covered products of nature. The Federal Circuit initially reversed, but on remand in light of *Mayo Collaborative Services* v. *Prometheus Laboratories, Inc.*, 566 U. S. ___, the Circuit found both isolated DNA and cDNA patent eligible.

Held: A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring. Pp. 10–18.

(a) The Patent Act permits patents to be issued to "[w]hoever invents or discovers any new and useful . . . composition of matter," §101, but "laws of nature, natural phenomena, and abstract ideas" "'are basic tools of scientific and technological work'" that lie beyond the domain of patent protection, *Mayo, supra,* at ___. The rule against patents on naturally occurring things has limits, however. Patent protection strikes a delicate balance between creating "incentives that lead to creation, invention, and discovery" and "imped[ing] the flow of information that might permit, indeed spur, invention." *Id.,* at ___. This standard is used to determine whether Myriad's patents claim a "new and useful . . . composition of matter," §101, or claim naturally occurring phenomena. Pp. 10–11.

(b) Myriad's DNA claim falls within the law of nature exception. Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes. *Diamond* v. *Chakrabarty*, 447 U. S. 303, is central to the patent-eligibility inquiry whether such action was new "with markedly different characteristics from any found in nature," *id.,* at 310. Myriad did not create or alter either the genetic information encoded in the BCRA1 and BCRA2 genes or the genetic structure of the DNA. It found an important and useful gene, but groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the §101 inquiry. See *Funk Brothers Seed Co.* v. *Kalo Inoculant Co.*, 333 U. S. 127. Finding the location of the BRCA1 and BRCA2 genes does not render the genes patent eligible "new . . . composition[s] of matter," §101. Myriad's patent descriptions highlight the problem with its claims: They detail the extensive process of discovery, but extensive effort alone is insufficient to satisfy §101's demands. Myriad's claims are not saved by the fact that isolating DNA from the human genome severs the chemical bonds that bind gene molecules together. The claims are not expressed in terms of chemical composition, nor do they rely on the chemical changes resulting from the isolation of a particular DNA section. Instead, they focus on the genetic information encoded in the BRCA1 and BRCA2 genes. Finally, Myriad argues that the Patent and Trademark Office's past practice of awarding gene patents is entitled to deference, citing *J. E. M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U. S. 124, a case where Congress had endorsed a PTO practice in subsequent legislation. There has been no such endorsement here, and the United States argued in the Federal Circuit and in this Court that isolated DNA was not patent eligible under §101. Pp. 12–16.

(c) cDNA is not a "product of nature," so it is patent eligible under §101. cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments. Its creation results in an exons-only molecule, which is not naturally occurring. Its order of the exons may be dictated by nature, but the lab technician unquestionably creates something new when introns are removed from a DNA sequence to make cDNA. Pp. 16–17.

(d) This case, it is important to note, does not involve method claims, patents on new applications of knowledge about the BRCA1 and BRCA2 genes, or the patentability of DNA in which the order of the naturally occurring nucleotides has been altered. Pp. 17–18.

689 F. 3d 1303, affirmed in part and reversed in part.

THOMAS, J., delivered the opinion of the Court, in which ROBERTS, C. J., and KENNEDY, GINSBURG, BREYER, ALITO, SOTOMAYOR, and KAGAN, JJ., joined, and in which SCALIA, J., joined in part. SCALIA, J., filed an opinion concurring in part and concurring in the judgment.

NOTICE: This opinion is subject to formal revision before publication in the preliminary print of the United States Reports. Readers are requested to notify the Reporter of Decisions, Supreme Court of the United States, Washington, D. C. 20543, of any typographical or other formal errors, in order that corrections may be made before the preliminary print goes to press.

SUPREME COURT OF THE UNITED STATES

No. 12–398

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL., PETITIONERS *v.* MYRIAD GENETICS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

[June 13, 2013]

JUSTICE THOMAS delivered the opinion of the Court.

Respondent Myriad Genetics, Inc. (Myriad), discovered the precise location and sequence of two human genes, mutations of which can substantially increase the risks of breast and ovarian cancer. Myriad obtained a number of patents based upon its discovery. This case involves claims from three of them and requires us to resolve whether a naturally occurring segment of deoxyribonucleic acid (DNA) is patent eligible under 35 U. S. C. §101 by virtue of its isolation from the rest of the human genome. We also address the patent eligibility of synthetically created DNA known as complementary DNA (cDNA), which contains the same protein-coding information found in a segment of natural DNA but omits portions within the DNA segment that do not code for proteins. For the reasons that follow, we hold that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but that cDNA is patent eligible because it is not naturally occurring. We, therefore, affirm in part and reverse in part the decision of

the United States Court of Appeals for the Federal Circuit.

I

A

Genes form the basis for hereditary traits in living organisms. See generally *Association for Molecular Pathology* v. *United States Patent and Trademark Office*, 702 F. Supp. 2d 181, 192–211 (SDNY 2010). The human genome consists of approximately 22,000 genes packed into 23 pairs of chromosomes. Each gene is encoded as DNA, which takes the shape of the familiar "double helix" that Doctors James Watson and Francis Crick first described in 1953. Each "cross-bar" in the DNA helix consists of two chemically joined nucleotides. The possible nucleotides are adenine (A), thymine (T), cytosine (C), and guanine (G), each of which binds naturally with another nucleotide: A pairs with T; C pairs with G. The nucleotide cross-bars are chemically connected to a sugar-phosphate backbone that forms the outside framework of the DNA helix. Sequences of DNA nucleotides contain the information necessary to create strings of amino acids, which in turn are used in the body to build proteins. Only some DNA nucleotides, however, code for amino acids; these nucleotides are known as "exons." Nucleotides that do not code for amino acids, in contrast, are known as "introns."

Creation of proteins from DNA involves two principal steps, known as transcription and translation. In transcription, the bonds between DNA nucleotides separate, and the DNA helix unwinds into two single strands. A single strand is used as a template to create a complementary ribonucleic acid (RNA) strand. The nucleotides on the DNA strand pair naturally with their counterparts, with the exception that RNA uses the nucleotide base uracil (U) instead of thymine (T). Transcription results in a single strand RNA molecule, known as pre-RNA, whose nucleotides form an inverse image of the DNA strand from which

it was created. Pre-RNA still contains nucleotides corresponding to both the exons and introns in the DNA molecule. The pre-RNA is then naturally "spliced" by the physical removal of the introns. The resulting product is a strand of RNA that contains nucleotides corresponding only to the exons from the original DNA strand. The exons-only strand is known as messenger RNA (mRNA), which creates amino acids through translation. In translation, cellular structures known as ribosomes read each set of three nucleotides, known as codons, in the mRNA. Each codon either tells the ribosomes which of the 20 possible amino acids to synthesize or provides a stop signal that ends amino acid production.

DNA's informational sequences and the processes that create mRNA, amino acids, and proteins occur naturally within cells. Scientists can, however, extract DNA from cells using well known laboratory methods. These methods allow scientists to isolate specific segments of DNA—for instance, a particular gene or part of a gene—which can then be further studied, manipulated, or used. It is also possible to create DNA synthetically through processes similarly well known in the field of genetics. One such method begins with an mRNA molecule and uses the natural bonding properties of nucleotides to create a new, synthetic DNA molecule. The result is the inverse of the mRNA's inverse image of the original DNA, with one important distinction: Because the natural creation of mRNA involves splicing that removes introns, the synthetic DNA created from mRNA also contains only the exon sequences. This synthetic DNA created in the laboratory from mRNA is known as complementary DNA (cDNA).

Changes in the genetic sequence are called mutations. Mutations can be as small as the alteration of a single nucleotide—a change affecting only one letter in the genetic code. Such small-scale changes can produce an entirely different amino acid or can end protein production alto-

gether. Large changes, involving the deletion, rearrangement, or duplication of hundreds or even millions of nucleotides, can result in the elimination, misplacement, or duplication of entire genes. Some mutations are harmless, but others can cause disease or increase the risk of disease. As a result, the study of genetics can lead to valuable medical breakthroughs.

B

This case involves patents filed by Myriad after it made one such medical breakthrough. Myriad discovered the precise location and sequence of what are now known as the BRCA1 and BRCA2 genes. Mutations in these genes can dramatically increase an individual's risk of developing breast and ovarian cancer. The average American woman has a 12- to 13-percent risk of developing breast cancer, but for women with certain genetic mutations, the risk can range between 50 and 80 percent for breast cancer and between 20 and 50 percent for ovarian cancer. Before Myriad's discovery of the BRCA1 and BRCA2 genes, scientists knew that heredity played a role in establishing a woman's risk of developing breast and ovarian cancer, but they did not know which genes were associated with those cancers.

Myriad identified the exact location of the BRCA1 and BRCA2 genes on chromosomes 17 and 13. Chromosome 17 has approximately 80 million nucleotides, and chromosome 13 has approximately 114 million. *Association for Molecular Pathology* v. *United States Patent and Trademark Office*, 689 F. 3d 1303, 1328 (CA Fed. 2012). Within those chromosomes, the BRCA1 and BRCA2 genes are each about 80,000 nucleotides long. If just exons are counted, the BRCA1 gene is only about 5,500 nucleotides long; for the BRCA2 gene, that number is about 10,200. *Ibid.* Knowledge of the location of the BRCA1 and BRCA2 genes allowed Myriad to determine their typical nucleotide

sequence.[1] That information, in turn, enabled Myriad to develop medical tests that are useful for detecting mutations in a patient's BRCA1 and BRCA2 genes and thereby assessing whether the patient has an increased risk of cancer.

Once it found the location and sequence of the BRCA1 and BRCA2 genes, Myriad sought and obtained a number of patents. Nine composition claims from three of those patents are at issue in this case.[2] See *id.*, at 1309, and n. 1 (noting composition claims). Claims 1, 2, 5, and 6 from the '282 patent are representative. The first claim asserts a patent on "[a]n isolated DNA coding for a BRCA1 polypeptide," which has "the amino acid sequence set forth in SEQ ID NO:2." App. 822. SEQ ID NO:2 sets forth a list of 1,863 amino acids that the typical BRCA1 gene encodes. See *id.*, at 785–790. Put differently, claim 1 asserts a patent claim on the DNA code that tells a cell to produce the string of BRCA1 amino acids listed in SEQ ID NO:2.

Claim 2 of the '282 patent operates similarly. It claims "[t]he isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1." *Id.,* at 822. Like SEQ ID NO:2, SEQ ID NO:1 sets forth a long list of data, in this instance the sequence of cDNA that codes for the BRCA1 amino acids listed in claim 1. Importantly, SEQ ID NO:1 lists only the cDNA exons in the BRCA1 gene, rather than a full DNA sequence containing both exons and introns. See *id.,* at 779 (stating that SEQ ID NO:1's "MOLECULE TYPE:" is "cDNA"). As a result, the Federal Circuit recognized that claim 2 asserts a patent on the cDNA nucleotide sequence listed in SEQ ID

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[1] Technically, there is no "typical" gene because nucleotide sequences vary between individuals, sometimes dramatically. Geneticists refer to the most common variations of genes as "wild types."

[2] At issue are claims 1, 2, 5, 6, and 7 of U. S. Patent 5,747,282 (the '282 patent), claim 1 of U. S. Patent 5,693,473 (the '473 patent), and claims 1, 6, and 7 of U. S. Patent 5,837,492 (the '492 patent).

NO:1, which codes for the typical BRCA1 gene. 689 F. 3d, at 1326, n. 9; *id.,* at 1337 (Moore, J., concurring in part); *id.,* at 1356 (Bryson, J., concurring in part and dissenting in part).

Claim 5 of the '282 patent claims a subset of the data in claim 1. In particular, it claims "[a]n isolated DNA having at least 15 nucleotides of the DNA of claim 1." App. 822. The practical effect of claim 5 is to assert a patent on any series of 15 nucleotides that exist in the typical BRCA1 gene. Because the BRCA1 gene is thousands of nucleotides long, even BRCA1 genes with substantial mutations are likely to contain at least one segment of 15 nucleotides that correspond to the typical BRCA1 gene. Similarly, claim 6 of the '282 patent claims "[a]n isolated DNA having at least 15 nucleotides of the DNA of claim 2." *Ibid.* This claim operates similarly to claim 5, except that it references the cDNA-based claim 2. The remaining claims at issue are similar, though several list common mutations rather than typical BRCA1 and BRCA2 sequences. See *ibid.* (claim 7 of the '282 patent); *id.,* at 930 (claim 1 of the '473 patent); *id.,* at 1028 (claims 1, 6, and 7 of the '492 patent).

C

Myriad's patents would, if valid, give it the exclusive right to isolate an individual's BRCA1 and BRCA2 genes (or any strand of 15 or more nucleotides within the genes) by breaking the covalent bonds that connect the DNA to the rest of the individual's genome. The patents would also give Myriad the exclusive right to synthetically create BRCA cDNA. In Myriad's view, manipulating BRCA DNA in either of these fashions triggers its "right to exclude others from making" its patented composition of matter under the Patent Act. 35 U. S. C. §154(a)(1); see also §271(a) ("[W]hoever without authority makes . . . any patented invention . . . infringes the patent").

But isolation is necessary to conduct genetic testing, and Myriad was not the only entity to offer BRCA testing after it discovered the genes. The University of Pennsylvania's Genetic Diagnostic Laboratory (GDL) and others provided genetic testing services to women. Petitioner Dr. Harry Ostrer, then a researcher at New York University School of Medicine, routinely sent his patients' DNA samples to GDL for testing. After learning of GDL's testing and Ostrer's activities, Myriad sent letters to them asserting that the genetic testing infringed Myriad's patents. App. 94–95 (Ostrer letter). In response, GDL agreed to stop testing and informed Ostrer that it would no longer accept patient samples. Myriad also filed patent infringement suits against other entities that performed BRCA testing, resulting in settlements in which the defendants agreed to cease all allegedly infringing activity. 689 F. 3d, at 1315. Myriad, thus, solidified its position as the only entity providing BRCA testing.

Some years later, petitioner Ostrer, along with medical patients, advocacy groups, and other doctors, filed this lawsuit seeking a declaration that Myriad's patents are invalid under 35 U. S. C. §101. 702 F. Supp. 2d, at 186. Citing this Court's decision in *MedImmune, Inc.* v. *Genentech, Inc.*, 549 U. S. 118 (2007), the District Court denied Myriad's motion to dismiss for lack of standing. *Association for Molecular Pathology* v. *United States Patent and Trademark Office*, 669 F. Supp. 2d 365, 385–392 (SDNY 2009). The District Court then granted summary judgment to petitioners on the composition claims at issue in this case based on its conclusion that Myriad's claims, including claims related to cDNA, were invalid because they covered products of nature. 702 F. Supp. 2d, at 220–237. The Federal Circuit reversed, *Association for Molecular Pathology* v. *United States Patent and Trademark Office*, 653 F. 3d 1329 (2011), and this Court granted the petition for certiorari, vacated the judgment, and re-

manded the case in light of *Mayo Collaborative Services* v. *Prometheus Laboratories, Inc.*, 566 U. S. ___ (2012). See *Association for Molecular Pathology* v. *Myriad Genetics, Inc.*, 566 U. S. ___ (2012).

On remand, the Federal Circuit affirmed the District Court in part and reversed in part, with each member of the panel writing separately. All three judges agreed that only petitioner Ostrer had standing. They reasoned that Myriad's actions against him and his stated ability and willingness to begin BRCA1 and BRCA2 testing if Myriad's patents were invalidated were sufficient for Article III standing. 689 F. 3d, at 1323; *id.,* at 1337 (opinion of Moore, J.); *id.,* at 1348 (opinion of Bryson, J.).

With respect to the merits, the court held that both isolated DNA and cDNA were patent eligible under §101. The central dispute among the panel members was whether the act of *isolating* DNA—separating a specific gene or sequence of nucleotides from the rest of the chromosome—is an inventive act that entitles the individual who first isolates it to a patent. Each of the judges on the panel had a different view on that question. Judges Lourie and Moore agreed that Myriad's claims were patent eligible under §101 but disagreed on the rationale. Judge Lourie relied on the fact that the entire DNA molecule is held together by chemical bonds and that the covalent bonds at both ends of the segment must be severed in order to isolate segments of DNA. This process technically creates new molecules with unique chemical compositions. See *id.*, at 1328 ("Isolated DNA . . . is a free-standing portion of a larger, natural DNA molecule. Isolated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule"). Judge Lourie found this chemical alteration to be dispositive, because isolating a particular strand of DNA creates a nonnaturally occurring molecule, even though the

chemical alteration does not change the information-transmitting quality of the DNA. See *id.,* at 1330 ("The claimed isolated DNA molecules are distinct from their natural existence as portions of larger entities, and their informational content is irrelevant to that fact. We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature"). Accordingly, he rejected petitioners' argument that isolated DNA was ineligible for patent protection as a product of nature.

Judge Moore concurred in part but did not rely exclusively on Judge Lourie's conclusion that chemically breaking covalent bonds was sufficient to render isolated DNA patent eligible. *Id.,* at 1341 ("To the extent the majority rests its conclusion on the chemical differences between [naturally occurring] and isolated DNA (breaking the covalent bonds), I cannot agree that this is sufficient to hold that the claims to human genes are directed to patentable subject matter"). Instead, Judge Moore also relied on the United States Patent and Trademark Office's (PTO) practice of granting such patents and on the reliance interests of patent holders. *Id.,* at 1343. However, she acknowledged that her vote might have come out differently if she "were deciding this case on a blank canvas." *Ibid.*

Finally, Judge Bryson concurred in part and dissented in part, concluding that isolated DNA is not patent eligible. As an initial matter, he emphasized that the breaking of chemical bonds was not dispositive: "[T]here is no magic to a chemical bond that requires us to recognize a new product when a chemical bond is created or broken." *Id.,* at 1351. Instead, he relied on the fact that "[t]he nucleotide sequences of the claimed molecules are the same as the nucleotide sequences found in naturally occurring human genes." *Id.,* at 1355. Judge Bryson then concluded that genetic "structural similarity dwarfs the significance

of the structural differences between isolated DNA and naturally occurring DNA, especially where the structural differences are merely ancillary to the breaking of covalent bonds, a process that is itself not inventive." *Ibid.* Moreover, Judge Bryson gave no weight to the PTO's position on patentability because of the Federal Circuit's position that "the PTO lacks substantive rulemaking authority as to issues such as patentability." *Id.,* at 1357.

Although the judges expressed different views concerning the patentability of isolated DNA, all three agreed that patent claims relating to cDNA met the patent eligibility requirements of §101. *Id.,* at 1326, and n. 9 (recognizing that some patent claims are limited to cDNA and that such claims are patent eligible under §101); *id.,* at 1337 (Moore, J., concurring in part); *id.,* at 1356 (Bryson, J., concurring in part and dissenting in part) ("cDNA cannot be isolated from nature, but instead must be created in the laboratory . . . because the introns that are found in the native gene are removed from the cDNA segment").[3] We granted certiorari. 568 U. S. ___ (2012).

II

A

Section 101 of the Patent Act provides:

> "Whoever invents or discovers any new and useful . . . composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

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[3]Myriad continues to challenge Dr. Ostrer's Declaratory Judgment Act standing in this Court. Brief for Respondents 17–22. But we find that, under the Court's decision in *MedImmune, Inc.* v. *Genentech, Inc.*, Dr. Ostrer has alleged sufficient facts "under all the circumstances, [to] show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." 549 U. S. 118, 127 (2007) (internal quotation marks omitted).

35 U. S. C. §101.

We have "long held that this provision contains an important implicit exception[:] Laws of nature, natural phenomena, and abstract ideas are not patentable." *Mayo*, 566 U. S., at ___ (slip op., at 1) (internal quotation marks and brackets omitted). Rather, "'they are the basic tools of scientific and technological work'" that lie beyond the domain of patent protection. *Id.,* at ___ (slip op., at 2). As the Court has explained, without this exception, there would be considerable danger that the grant of patents would "tie up" the use of such tools and thereby "inhibit future innovation premised upon them." *Id.*, at ___ (slip op., at 17). This would be at odds with the very point of patents, which exist to promote creation. *Diamond* v. *Chakrabarty*, 447 U. S. 303, 309 (1980) (Products of nature are not created, and "'manifestations . . . of nature [are] free to all men and reserved exclusively to none'").

The rule against patents on naturally occurring things is not without limits, however, for "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," and "too broad an interpretation of this exclusionary principle could eviscerate patent law." 566 U. S., at ___ (slip op., at 2). As we have recognized before, patent protection strikes a delicate balance between creating "incentives that lead to creation, invention, and discovery" and "imped[ing] the flow of information that might permit, indeed spur, invention." *Id.,* at ___ (slip op., at 23). We must apply this well-established standard to determine whether Myriad's patents claim any "new and useful . . . composition of matter," §101, or instead claim naturally occurring phenomena.

B

It is undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and

BRCA2 genes. The location and order of the nucleotides existed in nature before Myriad found them. Nor did Myriad create or alter the genetic structure of DNA. Instead, Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13. The question is whether this renders the genes patentable.

Myriad recognizes that our decision in *Chakrabarty* is central to this inquiry. Brief for Respondents 14, 23–27. In *Chakrabarty*, scientists added four plasmids to a bacterium, which enabled it to break down various components of crude oil. 447 U. S., at 305, and n. 1. The Court held that the modified bacterium was patentable. It explained that the patent claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" *Id.,* at 309–310 (quoting *Hartranft* v. *Wiegmann*, 121 U. S. 609, 615 (1887); alteration in original). The *Chakrabarty* bacterium was new "with markedly different characteristics from any found in nature," 447 U. S., at 310, due to the additional plasmids and resultant "capacity for degrading oil." *Id.,* at 305, n. 1. In this case, by contrast, Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.

Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the §101 inquiry. In *Funk Brothers Seed Co.* v. *Kalo Inoculant Co.*, 333 U. S. 127 (1948), this Court considered a composition patent that claimed a mixture of naturally occurring strains of bacteria that helped leguminous plants take nitrogen from the air and fix it in the soil. *Id.,* at 128–129. The ability of the bacteria to fix nitrogen was well known, and farmers commonly "inoculated" their crops with them to improve soil nitrogen

levels. But farmers could not use the same inoculant for all crops, both because plants use different bacteria and because certain bacteria inhibit each other. *Id.,* at 129–130. Upon learning that several nitrogen-fixing bacteria did not inhibit each other, however, the patent applicant combined them into a single inoculant and obtained a patent. *Id.,* at 130. The Court held that the composition was not patent eligible because the patent holder did not alter the bacteria in any way. *Id.,* at 132 ("There is no way in which we could call [the bacteria mixture a product of invention] unless we borrowed invention from the discovery of the natural principle itself"). His patent claim thus fell squarely within the law of nature exception. So do Myriad's. Myriad found the location of the BRCA1 and BRCA2 genes, but that discovery, by itself, does not render the BRCA genes "new . . . composition[s] of matter," §101, that are patent eligible.

Indeed, Myriad's patent descriptions highlight the problem with its claims. For example, a section of the '282 patent's Detailed Description of the Invention indicates that Myriad found the location of a gene associated with increased risk of breast cancer and identified mutations of that gene that increase the risk. See App. 748–749.[4] In

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[4] The full relevant text of the Detailed Description of the Patent is as follows:

"It is a discovery of the present invention that the BRCA1 locus which predisposes individuals to breast cancer and ovarian cancer, is a gene encoding a BRCA1 protein, which has been found to have no significant homology with known protein or DNA sequences. . . . It is a discovery of the present invention that mutations in the BRCA1 locus in the germline are indicative of a predisposition to breast cancer and ovarian cancer. Finally, it is a discovery of the present invention that somatic mutations in the BRCA1 locus are also associated with breast cancer, ovarian cancer and other cancers, which represents an indicator of these cancers or of the prognosis of these cancers. The mutational events of the BRCA1 locus can involve deletions, insertions and point mutations." App. 749.

subsequent language Myriad explains that the location of the gene was unknown until Myriad found it among the approximately eight million nucleotide pairs contained in a subpart of chromosome 17. See *Ibid.*[5] The '473 and '492 patents contain similar language as well. See *id.*, at 854, 947. Many of Myriad's patent descriptions simply detail the "iterative process" of discovery by which Myriad narrowed the possible locations for the gene sequences that it sought.[6] See, *e.g.*, *id.*, at 750. Myriad seeks to import these extensive research efforts into the §101 patent-eligibility inquiry. Brief for Respondents 8–10, 34. But extensive effort alone is insufficient to satisfy the demands of §101.

Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule. Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and

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Notwithstanding Myriad's repeated use of the phrase "present invention," it is clear from the text of the patent that the various discoveries *are* the "invention."

[5] "Starting from a region on the long arm of human chromosome 17 of the human genome, 17q, which has a size estimated at about 8 million base pairs, a region which contains a genetic locus, BRCA1, which causes susceptibility to cancer, including breast and ovarian cancer, has been identified." *Ibid.*

[6] Myriad first identified groups of relatives with a history of breast cancer (some of whom also had developed ovarian cancer); because these individuals were related, scientists knew that it was more likely that their diseases were the result of genetic predisposition rather than other factors. Myriad compared sections of their chromosomes, looking for shared genetic abnormalities not found in the general population. It was that process which eventually enabled Myriad to determine where in the genetic sequence the BRCA1 and BRCA2 genes reside. See, *e.g.*, *id.*, at 749, 763–775.

BRCA2 genes. If the patents depended upon the creation of a unique molecule, then a would-be infringer could arguably avoid at least Myriad's patent claims on entire genes (such as claims 1 and 2 of the '282 patent) by isolating a DNA sequence that included both the BRCA1 or BRCA2 gene and one additional nucleotide pair. Such a molecule would not be chemically identical to the molecule "invented" by Myriad. But Myriad obviously would resist that outcome because its claim is concerned primarily with the information contained in the genetic *sequence*, not with the specific chemical composition of a particular molecule.

Finally, Myriad argues that the PTO's past practice of awarding gene patents is entitled to deference, citing *J. E. M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U. S. 124 (2001). See Brief for Respondents 35–39, 49–50. We disagree. *J. E. M.* held that new plant breeds were eligible for utility patents under §101 notwithstanding separate statutes providing special protections for plants, see 7 U. S. C. §2321 *et seq.* (Plant Variety Protection Act); 35 U. S. C. §§161–164 (Plant Patent Act of 1930). After analyzing the text and structure of the relevant statutes, the Court mentioned that the Board of Patent Appeals and Interferences had determined that new plant breeds were patent eligible under §101 and that Congress had recognized and endorsed that position in a subsequent Patent Act amendment. 534 U. S., at 144–145 (citing *In re Hibberd*, 227 USPQ 443 (1985) and 35 U. S. C. §119(f)). In this case, however, Congress has not endorsed the views of the PTO in subsequent legislation. While Myriad relies on Judge Moore's view that Congress endorsed the PTO's position in a single sentence in the Consolidated Appropriations Act of 2004, see Brief for Respondents 31, n. 8; 689 F. 3d, at 1346, that Act does not even mention genes, much less isolated DNA. §634, 118 Stat. 101 ("None of the funds appropriated or otherwise made available under this

Act may be used to issue patents on claims directed to or encompassing a human organism").

Further undercutting the PTO's practice, the United States argued in the Federal Circuit and in this Court that isolated DNA was *not* patent eligible under §101, Brief for United States as *Amicus Curiae* 20–33, and that the PTO's practice was not "a sufficient reason to hold that isolated DNA is patent-eligible." *Id.,* at 26. See also *id.*, at 28–29. These concessions weigh against deferring to the PTO's determination.[7]

C

cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments. As already explained, creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring.[8] Petitioners concede that cDNA differs from natural DNA in that "the non-coding regions have

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[7] Myriad also argues that we should uphold its patents so as not to disturb the reliance interests of patent holders like itself. Brief for Respondents 38–39. Concerns about reliance interests arising from PTO determinations, insofar as they are relevant, are better directed to Congress. See *Mayo Collaborative Services* v. *Prometheus Laboratories, Inc.*, 566 U. S. ___, ___ (2012) (slip op., at 22–24).

[8] Some viruses rely on an enzyme called reverse transcriptase to reproduce by copying RNA into cDNA. In rare instances, a side effect of a viral infection of a cell can be the random incorporation of fragments of the resulting cDNA, known as a pseudogene, into the genome. Such pseudogenes serve no purpose; they are not expressed in protein creation because they lack genetic sequences to direct protein expression. See J. Watson et al., Molecular Biology of the Gene 142, 144, fig. 7–5 (6th ed. 2008). Perhaps not surprisingly, given pseudogenes' apparently random origins, petitioners "have failed to demonstrate that the pseudogene consists of the same sequence as the BRCA1 cDNA." *Association for Molecular Pathology* v. *United States Patent and Trademark Office*, 689 F. 3d 1303, 1356, n. 5 (CA Fed. 2012). The possibility that an unusual and rare phenomenon *might* randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter nonpatentable.

been removed." Brief for Petitioners 49. They nevertheless argue that cDNA is not patent eligible because "[t]he nucleotide sequence of cDNA is dictated by nature, not by the lab technician." *Id.,* at 51. That may be so, but the lab technician unquestionably creates something new when cDNA is made. cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived. As a result, cDNA is not a "product of nature" and is patent eligible under §101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.[9]

III

It is important to note what is *not* implicated by this decision. First, there are no method claims before this Court. Had Myriad created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent. But the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents "were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach," 702 F. Supp. 2d, at 202–203, and are not at issue in this case.

Similarly, this case does not involve patents on new *applications* of knowledge about the BRCA1 and BRCA2 genes. Judge Bryson aptly noted that, "[a]s the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are

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[9] We express no opinion whether cDNA satisfies the other statutory requirements of patentability. See, *e.g.*, 35 U. S. C. §§102, 103, and 112; Brief for United States as *Amicus Curiae* 19, n. 5.

limited to such applications." 689 F. 3d, at 1349.

Nor do we consider the patentability of DNA in which the order of the naturally occurring nucleotides has been altered. Scientific alteration of the genetic code presents a different inquiry, and we express no opinion about the application of §101 to such endeavors. We merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material.

* * *

For the foregoing reasons, the judgment of the Federal Circuit is affirmed in part and reversed in part.

It is so ordered.

SUPREME COURT OF THE UNITED STATES

No. 12–398

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL., PETITIONERS *v.* MYRIAD GENETICS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

[June 13, 2013]

JUSTICE SCALIA, concurring in part and concurring in the judgment.

I join the judgment of the Court, and all of its opinion except Part I–A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief. It suffices for me to affirm, having studied the opinions below and the expert briefs presented here, that the portion of DNA isolated from its natural state sought to be patented is identical to that portion of the DNA in its natural state; and that complementary DNA (cDNA) is a synthetic creation not normally present in nature.