**Monitoring International Trends**

**Posted July 2019**

The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

* Potential new product developments and applications;
* Global regulatory and blood practice trends;
* Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
* Other emerging risks that could put financial or other pressures on the Australian sector.

**Highlights Report**

Some recent matters of interest appear on pages 7 to 20. Highlights are listed below:

**Safety and Patient Blood Management (begins page 7)**

## Appropriate transfusion; bleeding risk (p7)

* + An international study has found that limiting perioperative blood transfusions around cardiac surgery showed no additional risk to patients when it comes to kidney injury.
  + A study by the US Centers for Disease Control and Prevention (CDC) found that an outbreak of sepsis was the result of the transfusion of apheresis platelets contaminated with Acinetobacter calcoaceticus–baumannii complex and Staphylococcus saprophyticus bacteria.
  + Researchers have investigated to what extent patients treated for depression with selective serotonin reuptake inhibitors experience higher blood loss and transfusion rates after total hip arthroplasty and total knee arthroplasty.
  + Researchers have evaluated the predictive value of coagulation biomarkers for massive transfusion in patients with pelvic fractures.
  + A study has found that longer red blood cell storage “was associated with a smaller increase in haemoglobin concentration after transfusion”.
  + Researchers have found that “platelet transfusions were not associated with increased risk of death in critically ill patients”.
  + Researchers found that in massively transfused paediatric trauma patients, higher fresh frozen plasma ratios were associated with lower 24-hour mortality. They found the platelet ratio not to be associated with mortality.
  + A study has concluded that “without considering the additional supply cost of implementing a freshest available RBC strategy for critical care patients, there is no evidence to suggest that the policy improves quality-of-life or reduces other costs compared with standard transfusion practice”.
  + For adult patients with chronic anaemia associated with cancer or other diagnosis, a study has found that “red blood cell transfusion is associated with a modest, but clinically important, improvement in walk test distance and fatigue score outcomes”.

## Other (p8)

* + New data showed paediatric patients (from birth to 17 years) treated with Xarelto (rivaroxaban) had a similar low risk of recurrent venous thromboembolism and similar rates of bleeding when compared with current standard anticoagulation therapy.
  + Researchers reported that among patients with atrial fibrillation prescribed warfarin, clinical risk scores for major bleeding and thrombotic events were more strongly associated with future events than any international normalized ratio (INR) metrics for warfarin.
  + A report has said that many people who take over-the-counter aspirin, because it can lessen the clotting action of platelets in the blood, should stop.
  + A new airless spray can deliver the clotting proteins fibrinogen and thrombin to stop mild to moderate surgical bleeding.

#### **Products and Treatments (begins page 9)**

## Treating haemophilia (p9)

* + At the International Society on Thrombosis and Haemostasis (ISTH) 2019 Congress in Melbourne in July:
    - Roche announced data from its Phase IIIb STASEY study of Hemlibra (emicizumab) in haemophilia A.
    - Casebia Therapeutics presented new research on a gene editing approach to manage production of Factor VIII.
    - Results were presented from two new interim analyses of Novo Nordisk’s nonacog beta pegol (N9-GP) in children.
    - Sobi (Swedish Orphan Biovitrum) presented data showing that people in Sweden with haemophilia have a substantially higher prescription rate for analgesics than the general population, along with a higher prescription rate for neuroleptics and anti-depressants.
    - CSL Behring supported the presentation of new data from its recombinant coagulation factor programs.
    - Sangamo released more data about its Pfizer-partnered haemophilia A gene therapy SB-525.
    - Octapharma presented an update on the clinical development plan and pre-clinical data for SubQ-8, its subcutaneous recombinant FVIII**.**
    - Data was presented from the completed Phase I/IIa EXTEN-A study of Sanofi Genzyme’s BIVV001 (rFVIIIFc-VWF-XTEN), its extended half-life factor for haemophilia A; and
    - ISTH announced the official launch of [Gene Therapy in Hemophilia: An ISTH Education Initiative.](https://c212.net/c/link/?t=0&l=en&o=2517168-1&h=2236851648&u=https%3A%2F%2Fgenetherapy.isth.org%2F&a=Gene+Therapy+in+Hemophilia%3A+An+ISTH+Education+Initiative.)

## Treating beta thalassemia and sickle cell disease (p12)

* + Scientists are testing red blood cell exchange transfusion in patients with sickle cell disease, hoping to reduce the need for hospitalizations and slow or reverse organ damage.
  + The European Hematology Association Congress was told that an investigational drug for sickle cell anaemia, IMR-687, is well-tolerated, and it shows signs of potential for lowering blood biomarkers.

## Treating other conditions (p13)

* + CSL Behring showcased clinical advances and insights in chronic inflammatory demyelinating polyneuropathy with Hizentra [human normal immunoglobulin, 20 per cent, subcutaneous].
  + Takeda announced new data from an ad-hoc analysis of the Phase III HELP Study, designed to evaluate the onset of action for Takhzyro (lanadelumab) during days 0-69 of treatment to prevent attacks of hereditary angioedema.

**Regulatory matters (begins page 14**

* + The US Food and Drug Administration (FDA) granted Novartis’ sickle cell disease drug crizanlizumab Priority Review.
  + The FDA approved a supplemental New Drug Application for avatrombopag (Doptelet) to treat adults with chronic immune thrombocytopenia whose response to a prior therapy has been insufficient.
  + Bayer HealthCare received orphan drug designation for its use of human monoclonal IgG2 antibody against tissue factor pathway inhibitor, for the treatment of haemophilia B.
  + Alexion Pharmaceuticals announced that the European Commission had approved Ultomiris(ravulizumab) for the treatment of some adult patients with paroxysmal nocturnal haemoglobinuria.
  + The FDA approved Grifols’ Xembify, a 20 per cent subcutaneously- administered immunoglobulin for primary immunodeficiencies.

**Market structure and company news (begins page 15)**

* + Roche again agreed to extend its deadline to acquire Spark Therapeutics, to give the US Federal Trade Commission time to clear the transaction.
  + Aptevo Therapeutics launched its new 3000 IU vial size for its coagulation factor IX recombinant (Ixinity) treatment for haemophilia B in the US market.
  + Hemoglobin Oxygen Therapeutics announced that abstracts related to the company’s clinical development program in liver transplantation had been presented at medical conferences. The Principal Investigator said: "Preliminary results demonstrate that machine perfusion technology using Hemopure, a novel synthetic oxygen carrying solution, safely increases the number of transplantable livers and with the added benefit of avoiding the need for human blood products. We are encouraged by the follow up survival data”.
  + Novartis had its gene therapy for spinal muscular atrophy (Zolgensma) approved by the FDA, but some insurance companies are reported to be restricting their coverage of the $US 2.1 million price tag.
  + Bio Marin said it is “one step closer to a potential regulatory submission” since the Phase III cohort of its gene therapy study in severe haemophilia A met pre-specified criteria for regulatory submissions in the US and Europe.

**Specific country events (begins p 16)**

* + The American Red Cross has been emphasising it has a critical blood shortage, with less than a five-day supply for most blood types. For other US blood banks too, supplies have been critically low.
  + In the US, too, Intravenous immunoglobulin supply is not meeting demand, and there are reports that even heavily dependent patients face having their supply for infusion rationed.
  + At over 700 US clinics advertising unproven stem cell treatments, about two-thirds of the clinicians may be physicians, but a recent study suggests they are often trained in specialties unrelated to the services they provide.
  + Pfizer announced that the recently resigned FDA commissioner Scott Gottlieb would be joining its board of directors.
  + The US Centers for Disease Control and Prevention (CDC) found that fewer than 40 per cent of people in the US have been screened for HIV. It recommends that all people 13 to 64 be tested at least once.
  + In the US Bayer voluntarily recalled two lots of Kogenate FS antihaemophilic factor (recombinant) 2000 IU vials after a labelling issue.
  + Canada has a plasma shortage and immunoglobulin is reported to be in short supply.
  + On 20 June, Canadian Blood Services live streamed its board meeting as well as inviting the public to attend in Toronto.
  + The Indian government is establishing, in the poorest districts across the country, specialist laboratories to conduct tests for genetic diseases, a leading cause of death among infants and children.
  + In Australia, rural leaders have warned that in the current dusty conditions Q fever could be affecting more farmers.
  + Australia’s Therapeutic Goods Administration (TGA) has expanded its oversight of stem cell treatments in response to “concerns about some providers offering unproven and harmful treatments.”
  + May 2019 saw the release of the Australian Guidelines for the Prevention and Control of Infection in Healthcare.
  + Public Health England has advised Islamic pilgrims from Britain participating in the Haj to avoid camels due to a potential risk of contracting Middle East Respiratory Syndrome coronavirus (MERS-CoV). It also warned against products such as raw camel milk.
  + In the UK, the National Institute for Health and Care Excellence (NICE) recommended Merck's Prevymis (letermovir) for routine access for the prevention of cytomegalovirus reactivation and disease in patients who have undergone an allogeneic hematopoietic stem cell transplant.
  + The European Union and the US have fully implemented a mutual recognition agreement for inspections of manufacturing on bio- pharmaceutical sites for certain human medicines in their respective territories.

**Research not included elsewhere (begins page 18)**

* + Scientists at the Versiti Blood Research Institute in Milwaukee have a grant from the US National Institutes of Health to study Von Willebrand disease with the goal of improving diagnosis and treatment.
  + A recent paper has examined the effects of storage on blood plasma, from the viewpoint of its suitability for research.
  + Researchers in Japan and the US say they have found an inexpensive and effective way to grow large numbers of haematopoietic stem cells in the lab.
  + Researchers have reported on the development of molecular tools to aid accurate diagnosis of inherited blood disorders, along with recent improvements in this field.

**Infectious diseases (begins page 19)**

## Mosquito-borne diseases (p19)

* + Ontera received a contract from the US government's Intelligence Advanced Research Projects Activity (IARPA) to develop a point-of-care molecular test for Zika.
  + The Philippines declared a National Dengue Alert.
  + New research suggests that malaria could spread in somewhat cooler climates than might be expected, and this would reinforce the effect of climate change in extending the geographic areas where malaria is endemic.
  + Scientists at Duke University have been researching how human liver genes affect malaria’s growth, suggesting new ways to stop malaria before it spreads to the bloodstream.
  + According to results from a systematic review and meta-analysis, as many as 1 in 10 healthy blood donors globally may carry malaria parasites, making transfusion-transmitted malaria one of the most common transfusion- associated infections.

## Influenza (p20)

* + The World Health Organisation (WHO) reported that in Australia, H3N2 has been the dominant strain in the flu season.
  + A Phase III trial has shown that Roche’s Xofluza is well tolerated in children with flu.

## Ebola virus disease (p20)

* + WHO declared the Ebola outbreak in the Democratic Republic of Congo to be an international emergency.

## MERS-CoV (p20)

* + WHO said on 22 July that the number of confirmed cases of MERS since April 2012 had been 2,449, of which 845 at least had been fatal.

## Other diseases (p20)

* + A randomized trial found that patients who underwent autologous haematopoietic stem cell transplantation (HSCT) and received GSK’s recombinant *herpes zoster* vaccine (Shingrix) had a lower incidence of the illness compared with HSCT patients receiving placebo.
  + In the US this year 1,148 measles cases were recorded up to 22 July, across 30 states with the largest concentration being 623 in Brooklyn. Europe had reported 34,300 measles cases between 1 January and 7 May.
  + With the Hajj, or annual pilgrimage to Mecca, occurring from 9-14 August, 2 million pilgrims from over 183 countries were expected in Saudi Arabia, and the Ministry of Health in the Kingdom, along with officials in source countries, were recommending/ requiring all travellers be up to date with vaccinations.

**Detailed Report**

Contents

[1. Safety and patient blood management 7](#_Toc13746877)

[Appropriate Transfusion; Bleeding Risk 7](#_Toc13746878)

[Other 8](#_Toc13746879)

[2. Products and treatments 9](#_Toc13746880)

[Treating haemophilia 9](#_Toc13746881)

[Treating beta thalassemia and sickle cell disease 12](#_Toc13746882)

[Treating other conditions 13](#_Toc13746883)

[3. Regulatory 14](#_Toc13746884)

[4. Market structure and company news 15](#_Toc13746885)

[5. Specific country events 16](#_Toc13746886)

[6. Research not included elsewhere 18](#_Toc13746887)

[7. Infectious diseases 19](#_Toc13746888)

[Mosquito-borne diseases 19](#_Toc13746889)

[Influenza 20](#_Toc13746890)

[Ebola virus disease 20](#_Toc13746891)

[MERS-CoV 20](#_Toc13746892)

[Other diseases 20](#_Toc13746893)

# Safety and patient blood management

*We follow current issues in patient safety and achieving favourable patient outcomes.*

## Appropriate Transfusion; Bleeding Risk

* + An international study[[1]](#footnote-1) has found that limiting perioperative blood transfusions around cardiac surgery showed no additional risk to patients when it comes to kidney injury (twenty per cent of patients who undergo cardiopulmonary bypass surgery are said to experience some degree of kidney injury). The study considered 4,531 high-risk patients undergoing cardiopulmonary bypass surgery across 73 sites in 19 countries. One group was transfused only if their haemoglobin dipped below 7.5 grams per decilitre. The other group was transfused if their haemoglobin was less than 9.5 grams per decilitre. On average, patients in the restrictive group received 38 per cent fewer transfusions than those in the liberal group. The restrictive group did not have a higher rate of acute kidney injury.
  + A study[[2]](#footnote-2) by the US Centers for Disease Control and Prevention (CDC) found that an outbreak of sepsis was the result of the transfusion of apheresis platelets contaminated with Acinetobacter calcoaceticus–baumannii complex (ACBC) and Staphylococcus saprophyticus bacteria. The cluster of incidents, which occurred from May to October 2018, affected four patients from three states; one patient died.
  + Researchers have investigated[[3]](#footnote-3) to what extent patients treated for depression with selective serotonin reuptake inhibitors (SSRI’s) experience higher blood loss and transfusion rates after total hip arthroplasty (THA) and total knee arthroplasty (TKA)[[4]](#footnote-4). For SSRI users, the transfusion rate was 3.9 per cent in the TKA group and 8.5 per cent in the THA group. After controlling for a number of relevant factors, SSRI use was found to predict transfusion, particularly with THA. The authors concluded: “This represents an important factor that may be modified in the setting of total joint arthroplasty, but further work will be necessary to study potential alternative medications for depression in the perioperative phase.”
  + Researchers[[5]](#footnote-5) have evaluated the predictive value of coagulation biomarkers for the necessity for massive transfusion[[6]](#footnote-6) in patients with pelvic fractures. They concluded: “The results of the study indicated that fibrinogen levels on admission can be an independent predictor of massive transfusion in patients with pelvic fractures. The optimal cut-off value of fibrinogen for massive transfusion prediction in this study was 193.0 mg/dL.”
  + A study[[7]](#footnote-7) has found that longer red blood cell storage “was associated with a smaller increase in hemoglobin concentration after transfusion. Although statistically significant, the effect was modest, and its clinical relevance in subgroups of patients should be investigated in prospective clinical trials”.
  + Researchers[[8]](#footnote-8) examined the association between platelet transfusions and mortality in a large intensive care unit and found that “platelet transfusions were not associated with increased risk of death in critically ill patients” but suggested further studies are needed to determine subgroups for which the procedure may be beneficial.
  + Researchers**[[9]](#footnote-9)** found that in massively transfused paediatric trauma patients, higher fresh frozen plasma ratios were associated with lower 24-hour mortality. They found the platelet ratio not to be associated with mortality. They commented: “Although these findings represent the largest study evaluating blood product ratios in pediatric trauma patients, prospective studies are necessary to determine the optimum blood product ratios to minimize mortality in this population”.
  + A study**[[10]](#footnote-10)** across 59 intensive care units in five countries has introduced an economic evaluation into a consideration of transfusing red blood cells of different storage durations. It concluded that “without considering the additional supply cost of implementing a freshest available RBC strategy for critical care patients, there is no evidence to suggest that the policy improves quality-of-life or reduces other costs compared with standard transfusion practice”.
  + Patients with chronic anaemia associated with cancer or other diagnosis may be given red blood cell transfusions as an outpatient. A recent study set out to measure the effect of such transfusions on functional capacity and quality of life[[11]](#footnote-11). The researchers concluded that “red blood cell transfusion is associated with a modest, but clinically important improvement in walk test distance and fatigue score outcomes in adult hematology/oncology outpatients”.

## Other

* + At the 27th Congress of the International Society on Thrombosis and Haemostasis (ISTH) in Melbourne The Janssen Pharmaceutical Companies of Johnson & Johnson announced new results from the Phase III EINSTEIN-Jr study. This is the largest paediatric trial conducted for the treatment of blood clots or venous thromboembolism (VTE) and the first to evaluate a direct oral anticoagulant in a paediatric population. Data showed paediatric patients (from birth to 17 years) treated with Xarelto (rivaroxaban) had a similar low risk of recurrent venous thromboembolism (VTE) and similar rates of bleeding when compared with current standard anticoagulation therapy. The efficacy and safety profile of Xarelto in a paediatric population with VTE was shown to be comparable to that found in previous studies of adults with VTE. Christoph Male, Department of Paediatrics, Medical University of Vienna, said: "The EINSTEIN-Jr study with rivaroxaban represents a significant advance for paediatric VTE treatment."
  + Researchers reported[[12]](#footnote-12) that among patients with atrial fibrillation prescribed warfarin, clinical risk scores for major bleeding and thrombotic events were more strongly associated with future events than any international normalized ratio (INR) metrics for warfarin.
  + A study[[13]](#footnote-13) from doctors at Harvard and Beth Israel Deaconess Medical Center said that many people who take over-the-counter aspirin, because it can lessen the clotting action of platelets in the blood, should stop. New guidelines issued by the American Heart Association in March recommended that only those with history of heart disease, prior history of heart attack, or certain groups of healthy people between the ages of 40 to 70 should take a daily aspirin— and it should be done under the care of a doctor[[14]](#footnote-14).
  + When standard bleeding control techniques, such as sutures, are impractical, a new airless spray can deliver the clotting proteins fibrinogen and thrombin to stop mild to moderate surgical bleeding. The Ethicon Endo-Surgery Vistaseal Open and Laparoscopic dual applicators (available in 35 cm and 45 cm lengths) were designed in collaboration with Grifols, which developed the human fibrin sealant. Johnson & Johnson, the parent company of Ethicon, estimates that between one- and two-thirds of open surgery procedures experience disruptive bleeding events.

# Products and treatments

*Here the NBA follows the progress in research and clinical trials that may, within a reasonable timeframe, either make new products and treatments available or may lead to new uses or changes in use for existing products.*

## Treating haemophilia

* + At the International Society on Thrombosis and Haemostasis (ISTH) 2019 Congress in Melbourne in July, Roche supported 21 abstracts from its haemophilia programme, including five oral presentations. It announced data from its Phase IIIb STASEY study[[15]](#footnote-15) of Hemlibra (emicizumab) in haemophilia A, reinforcing the safety profile of the drug seen in the HAVEN 1 clinical trial[[16]](#footnote-16).
  + At the ISTH Congress, [Casebia Therapeutics](https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fcasebia.com%2F&esheet=52009603&newsitemid=20190708005187&lan=en-US&anchor=Casebia+Therapeutics&index=1&md5=0f53629db9efc7fd10fd9b76e9968965) presented new research on a gene editing approach to manage production of Factor VIII. Principal Scientist Alan Brooks reported findings that stable, titratable expression of FVIII in mice using CRISPR/Cas9 gene editing had been demonstrated[[17]](#footnote-17). Jim Burns, President and CEO of Casebia, said: “While acknowledging that early-stage results in animal models do not always translate into successful human treatments, we are extremely encouraged by the results.”
  + At the ISTH Congress, results from two new interim analyses[[18]](#footnote-18) of Novo Nordisk’s nonacog beta pegol (N9-GP) in children showed low annual bleeding rates, and that the drug was well tolerated[[19]](#footnote-19).
  + Sobi (Swedish Orphan Biovitrum) presented data to the ISTH Congress showing that people in Sweden with haemophilia have a substantially higher prescription rate for analgesics than the general population, along with a higher prescription rate for neuroleptics and anti-depressants. The data showed a similar prescription pattern among female carriers of haemophilia[[20]](#footnote-20).
  + At the ISTH Congress, CSL Behring supported the presentation of new data from its recombinant coagulation factor programs[[21]](#footnote-21), with one oral presentation[[22]](#footnote-22), nine research posters[[23]](#footnote-23) and six “real world evidence posters”[[24]](#footnote-24). The company also supported two satellite symposiums[[25]](#footnote-25).
  + At the ISTH Congress, Sangamo released more data about its Pfizer-partnered haemophilia A[[26]](#footnote-26) gene therapy SB-525. This demonstrated persistent longer-term responses and promising but early results in two further patients receiving the highest dose[[27]](#footnote-27). However, only one of the recently dosed patients had by then reached normal levels of factor VIII, and there was another case of liver enzyme elevation that had been detected before. Sangamo is confident of managing such events, but still must prove its product is safe, with an effective and long- lasting response.[[28]](#footnote-28)
  + At the ISTH Congress, Octapharma presented an update on the clinical development plan and pre-clinical data for SubQ-8, its subcutaneous recombinant FVIII**.** To facilitate uptake into the bloodstream, SubQ-8 combines simoctocog alfa, a human cell line-derived recombinant FVIII, with a recombinant von Willebrand factor fragment dimer produced in a human cell line. Larisa Belyanskaya, Head of Octapharma’s Haematology International Business Unit, said “We are very pleased with the promising preclinical data with SubQ-8 and its reception within the haemophilia community[[29]](#footnote-29)”. The Congress coincided with the enrolment of the first patient in a phase I/II study of SubQ-8 in previously treated haemophilia A patients.
  + At the ISTH Congress, an oral presentation revealed positive data from the completed Phase I/IIa EXTEN-A study[[30]](#footnote-30) of BIVV001 (rFVIIIFc-VWF-XTEN) This demonstrated that a single 65 IU/kg dose of the drug resulted in average factor activity levels of 17 per cent at seven days post infusion and significantly extended the half-life of factor VIII to 43 hours. Mouhamed Gueye, Head of Global Medical Affairs, Rare Blood Disorders, Sanofi Genzyme, said: “these early clinical results support the continued development of BIVV001.” BIVV001 was recently awarded Orphan Drug status by the European Commission.
  + At its Melbourne Congress,  [The International Society on Thrombosis and Haemostasis (ISTH)](https://c212.net/c/link/?t=0&l=en&o=2517168-1&h=257422283&u=http%3A%2F%2Fwww.isth.org%2F&a=The+International+Society+on+Thrombosis+and+Haemostasis+(ISTH)) announced the official launch of [Gene Therapy in Hemophilia: An ISTH Education Initiative.](https://c212.net/c/link/?t=0&l=en&o=2517168-1&h=2236851648&u=https%3A%2F%2Fgenetherapy.isth.org%2F&a=Gene+Therapy+in+Hemophilia%3A+An+ISTH+Education+Initiative.) The initiative is supported by grants from BioMarin, Pfizer, Shire, Spark Therapeutics and uniQure. See <https://genetherapy.isth.org/>. Earlier in the year, the ISTH Gene Therapy for Hemophilia Steering Committee, led by Flora Peyvandi and David Lillicrap, had surveyed the global haemophilia healthcare community to identify unmet educational needs specific to gene therapy in haemophilia[[31]](#footnote-31). The survey results were presented in a poster session on 7 July, *Gene Therapy Knowledge and Perceptions: Results of an International ISTH Survey.* The detailed roadmap developed for education was presented during a theatre session.
  + A study[[32]](#footnote-32) has suggested that [Bayer](https://www.bayer.com/)’s [Jivi](https://www.jivi-us.com), a FVIII replacement therapy for haemophilia A, has a longer half-life and a slower clearance from blood circulation than [Eloctate](https://www.eloctate.com/)[[33]](#footnote-33), and may protect against bleeding for longer periods.
  + A study[[34]](#footnote-34) has compared adjusted annualized bleeding rates between Bayer’s extended half-life recombinant factor VIII with three other prophylactic FVIII products for haemophilia, and found Bayer 94-9027 demonstrated similar adjusted bleeding rates to the other products, with lower utilization.

## Treating beta thalassemia and sickle cell disease

* + Scientists at the [University of Pittsburgh](http://www.pitt.edu) (Pitt) will use a $US19.2 million [National Institutes of Health](http://www.nih.gov) grant to test [red blood cell exchange transfusion](https://www.nm.org/conditions-and-care-areas/treatments/red-blood-cell-exchange) in patients with [sickle cell disease](https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease) (SCD),hoping to reduce the need for hospitalizations and to slow or reverse organ damage[[35]](#footnote-35). The international clinical trial[[36]](#footnote-36) is called [Sickle Cell Disease and Cardiovascular Risk – Red Cell Exchange](https://www.researchgate.net/grant/1-2-Sickle-Cell-Disease-and-CardiovAscular-Risk-Red-cell-Exchange-Trial-SCD-CARRE-Trial_3452732) (SCD-CARRE). The study’s principal investigator is Mark Gladwin, chair of medicine at Pitt’s [School of Medicine](https://www.medschool.pitt.edu/). This trial will determine whether red cell exchange should be added to the standard of care for high-risk patients. Patients will be randomly chosen to receive, for a year, either the current standard of care alone or combined with monthly red blood cell exchange treatments.
  + The [24th Congress of the European Hematology Association (EHA)](https://ehaweb.org/congress/previous-congresses/eha24/key-information/)[[37]](#footnote-37) was told that [Imara](http://imaratx.com)’s investigational drug for sickle cell anaemia [IMR-687](http://imaratx.com/our-programs/imr-687/) is well-tolerated, and shows signs of potential for lowering blood biomarkers. Imara’s CEO, Rahul D. Ballal, commented in a [press release](http://imaratx.com/imara-presented-positive-interim-phase-2a-data-on-imr-687-for-the-treatment-of-sickle-cell-disease-at-the-24th-congress-of-the-european-hematology-association/): “We are encouraged by this interim Phase 2a analysis that reinforces our belief in the potential of IMR-687 as a single oral, once-a-day therapeutic.” IMR-687 is an oral inhibitor of the [phosphodiesterase 9](https://www.ncbi.nlm.nih.gov/pubmed/24746902) (PDE9) enzyme in red blood cells. Inhibition of this enzyme in [preclinical studies](https://sicklecellanemianews.com/2016/12/08/imara-presents-results-imr-687-ash-meeting/) with cells and animal models showed that IMR-687 increases foetal haemoglobin, decreasing red cell sickling and [blood vessel occlusion](https://sicklecellanemianews.com/vaso-occlusive-crisis/). The drug has been [granted fast track designation](https://sicklecellanemianews.com/2019/05/30/fda-grants-fast-track-status-to-imaras-imr-687-candidate-therapy-for-sickle-cell-disease/) by the US Food and Drug Administration (FDA)[[38]](#footnote-38).

## Treating other conditions

* + At the 2019 Peripheral Nerve Society**[[39]](#footnote-39)** Annual Meeting**[[40]](#footnote-40)** CSL Behring showcased clinical advances and insights in chronic inflammatory demyelinating polyneuropathy (CIDP)**[[41]](#footnote-41)** with Hizentra [human normal immunoglobulin, 20 per cent, subcutaneous]. [CSL Behring](https://www.biospace.com/employer/521396/csl-behring/) supported the presentation of eight scientific posters. Presentations include new analysis from the PATH (Polyneuropathy and Treatment with Hizentra) study**,** new insights from the PATH trial extension, including long-term Quality of Life (QoL) and outcomes data analyses, and evaluation of IgG levels as a possible biomarker to predict treatment response. A further CSL Behring-supported presentation assessed the impact of CIDP diagnosis delay (after incident symptoms) on physical function. CSL Behring also hosted a symposium, *Navigating Diagnosis and Treatment Challenges in CIDP****[[42]](#footnote-42)****.*
  + At the Lisbon Congress of the European Academy of Allergy and Clinical Immunology Takeda announced new data from an ad-hoc analysis of the Phase III HELP Study[[43]](#footnote-43), designed to evaluate the onset of action for Takhzyro (lanadelumab) during days 0-69 of treatment to prevent attacks of hereditary angioedema. The analysis suggests that the drug begins to prevent hereditary angioedema attacks during this early treatment, with patients experiencing an 80.1 per cent decrease in mean monthly attack rate compared with placebo[[44]](#footnote-44).
  + At the C1 Inhibitor Deficiency and Angioedema Workshop in Budapest, data was presented on KalVista Pharmaceuticals’ KVD900, an oral selective inhibitor of plasma kallikrein, a possible target in hereditary angioedema, or HAE. Andrew Crockett, Chief Executive Officer of KalVista, said: “We believe KVD900 represents a new therapeutic opportunity to rapidly halt HAE attacks at their earliest sign and we look forward to seeing the Phase data late this year.”

# Regulatory

*The NBA monitors overseas regulatory decisions on products, processes or procedures which are or may be of relevance to its responsibilities.*

* + The FDA has granted Novartis’ sickle cell disease drug crizanlizumab Priority Review based on Phase II data showing prevention of vaso-occlusive crises in patients with sickle cell disease. Priority Review shortens the FDA review time to six months from the standard ten months.
  + The FDA approved a supplemental New Drug Application for avatrombopag (Doptelet) to treat adults with chronic immune thrombocytopenia whose response to a prior therapy has been insufficient[[45]](#footnote-45).
  + Bayer HealthCare in June received [orphan drug designation](https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=685719) for its use of its human monoclonal IgG2 antibody against tissue factor pathway inhibitor, for the treatment of haemophilia B. It had received a similar designation in March for using the approach to treat haemophilia A.
  + [Alexion Pharmaceuticals, Inc.](https://nam04.safelinks.protection.outlook.com/?url=https%3A%2F%2Fcts.businesswire.com%2Fct%2FCT%3Fid%3Dsmartlink%26url%3Dhttp%253A%252F%252Fwww.alexion.com%252F%26esheet%3D52006145%26newsitemid%3D20190703005355%26lan%3Den-US%26anchor%3DAlexion%2BPharmaceuticals%252C%2BInc.%26index%3D1%26md5%3Db93a3697b54ad1530ac0dbab54c626df&data=02%7C01%7C%7Ce4db08cc10514a7cb34d08d703f3aceb%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636982217430243548&sdata=Edy8YgOKNhtbHJfYj4J1Q9XhdMJwkYCK5r1Dl5%2BxHlc%3D&reserved=0) announced on 3 July that the European Commission had approved Ultomiris(ravulizumab) — a long-acting C5 complement inhibitor administered every eight weeks — for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) with haemolysis and with clinical symptoms indicative of high disease activity, and also for adult patients who are clinically stable after having been treated with Soliris (eculizumab) for at least the previous six months.The European Commission approval was based on results from two Phase III studies[[46]](#footnote-46).
  + The FDA approved Grifols’ Xembify, a 20 per cent subcutaneously- administered immunoglobulin for primary immunodeficiencies. The approval includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott- Aldrich syndrome and severe combined immunodeficiencies. The company plans to launch Xembify in the US in the last quarter of the year and is working to obtain additional approvals in Canada, Europe and elsewhere.

# Market structure and company news

*The NBA’s business intelligence follows company profitability, business forecasts, capital raisings or returns, mergers and takeovers, arrangements for joint research and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.*

* + [Roche](https://www.biospace.com/employer/547147/roche/) has again agreed to extend its deadline to acquire [Spark Therapeutics](https://www.biospace.com/employer/398039/spark-therapeutics/), to give the US Federal Trade Commission time to clear the transaction. The new deadline is 30 April 2020. Spark’s gene therapy program for haemophilia A is one reason Roche remains interested in completing the deal.
  + Grifols has been selected by Soludia Maghreb, a provider of haemodialysis solutions headquartered in Morocco, as the main supplier for a new manufacturing plant in northern Africa. Grifols will develop, build and automate the main process equipment for the IV solutions line.  The plant is expected to begin operations next year. This is the first industrial project for Grifols on the African continent.
  + Aptevo Therapeutics announced[[47]](#footnote-47) the launch of its new 3000 IU vial size for its coagulation factor IX recombinant (Ixinity) treatment for haemophilia B in the US market.
  + Hemoglobin Oxygen Therapeutics announced that abstracts related to the company’s clinical development program in liver transplantation were presented at May meetings of the International Liver Transplantation Society and of the European Surgical Association. Principal Investigator, Professor Robert J. Porte[[48]](#footnote-48) said: "Preliminary results demonstrate that machine perfusion technology using Hemopure, a novel synthetic oxygen carrying solution, safely increases the number of transplantable livers and with the added benefit of avoiding the need for human blood products. We are encouraged by the follow up survival data which has exceeded the study protocol and shows that all 11 patients remain alive with the longest being at 20 months after surgery[[49]](#footnote-49)."
  + Novartis had its gene therapy for spinal muscular atrophy (Zolgensma) approved by the FDA, but some insurance companies are reported to be restricting their coverage of the $US 2.1 million price tag[[50]](#footnote-50). Novartis had earlier said it would work with payers to develop outcomes-based payments spread over five years.
  + BioMarin announced on 28 May that the Phase III cohort of its valoctocogene roxaparvovec, gene therapy study in severe haemophilia A met pre-specified criteria for regulatory submissions in the US and Europe. Hank Fuchs, president of Worldwide Research and Development at BioMarin, said: “Reaching this pre-specified clinical endpoint is an important milestone that brings us one step closer to a potential regulatory submission.”[[51]](#footnote-51)

# Specific country events

* + The American Red Cross has been emphasising it has a critical blood shortage as donations drop during the summer as people go on vacation. It has asked for donations of blood and platelets. On 9 July there was less than a three-day supply for most blood types. The Red Cross says it needs a five-day supply. For other US blood banks too, supplies have been critically low and new donors are being sought, with some appeals offering tangible incentives such as raffle tickets.
  + In the US intravenous immunoglobulin supply is not meeting demand, and there are reports that even heavily dependent patients (for example those with primary immunodeficiency) face having their supply for infusion rationed. This situation appears to arise from both an insufficiency of source plasma and from the fact that immunoglobulin is being used for an increasing range of conditions, some of them off-label and without a significant evidence base. There have also been some supply interruptions, supposedly over quality issues.
  + At over 700 US clinics advertising unproven stem cell treatments, about two-thirds of the clinicians may be physicians, but a recent study[[52]](#footnote-52) suggests they are often trained in specialties unrelated to the services they provide.
  + On 28 June, Pfizer [announced](https://investors.pfizer.com/investor-news/press-release-details/2019/Scott-Gottlieb-Elected-to-Pfizers-Board-of-Directors/default.aspx) that the recently resigned US Food and Drug Administration commissioner Scott Gottlieb would be joining its board of directors. Commentators point to a pattern: [9 out of the last 10](https://twitter.com/walidgellad/status/1144427467844784133) FDA commissioners—almost four decades of its leadership—have gone on to work for pharmaceutical companies[[53]](#footnote-53).
  + The US Centers for Disease Control and Prevention (CDC) found[[54]](#footnote-54) that fewer than 40 per cent of people in the US have been screened for HIV. It recommends that all people 13 to 64 be tested at least once. Dr. Eugene McCray, director of the CDC's Division of HIV/AIDS Prevention, said: "Getting tested for HIV is quicker and easier than ever before -- and when you take the test, you take control. It's my hope that through the initiative to end the HIV epidemic, we will increase testing and early diagnosis, speed linkages to care, and help ensure rapid treatment is available to help save lives and prevent new HIV infections."[[55]](#footnote-55)
  + In the US Bayer voluntarily recalled two lots of Kogenate FS antihaemophilic factor (recombinant) 2000 IU vials after certain vials from these two lots that were labelled as Kogenate FS actually contained the FVIII hemophilia A treatment, Jivi, antihaemophilic factor (recombinant) PEGylated-aucl 3000 IU.
  + Canada has a plasma shortage and immunoglobulin is reported to be in short supply.
  + On 20 June, Canadian Blood Services live streamed its board meeting at [blood.ca,](https://www.globenewswire.com/Tracker?data=VFU1wkARDdS-YrnnondghR4uBaVOhiNagAecjXqmjJeOVzSH2SXYUZ97iaJVwjUBu_tBDYmBTpSGT2Agj1nmDgSLMu9lZQ3W4bfC1TfTWcjfMj2kTYp_0Qs6HMS6yZaAabPzhcWzvl6kYElj1rljJQ==) as well as inviting the public to attend in person in Toronto. It invites public participation in open board meetings twice a year.
  + The Indian government is establishing, in the poorest districts across the country, specialist laboratories to conduct tests for genetic diseases, a leading cause of death among infants and children. Amongst common genetic disorders in India are beta-thalassemia, sickle cell anaemia, haemophilia, cystic fibrosis, and spinal muscular atrophy.
  + In Australia, rural leaders have warned that in the current dusty conditions Q fever could be affecting more farmers. The disease can kill through septicaemia and pneumonia, but NSW Farmers president James Jackson said non-acute cases could lead to long-running chronic fatigue syndrome, consequent depression and suicide. There is a vaccine, but it requires a three-stage process involving a blood test and skin test, and the process can cost up to $500. “It’s a cost impediment for some people, and they’re not protecting themselves from this disease because it’s not on the PBS[[56]](#footnote-56),” Mr Jackson said. A Department of Health spokesman said the federal government provided vaccine manufacturer Seqirus with “significant funding” to ensure the ongoing production and supply on the open market of Q fever vaccine and test kits. He said: “To date, Seqirus has not sought a recommendation from the Pharmaceutical Benefits Advisory Committee to have their Q‑Vax vaccine for Q fever listed either on the Pharmaceutical Benefits Scheme or National Immunisation Program”.
  + Australia’s Therapeutic Goods Administration (TGA) has expanded its oversight of stem cell treatments in response to “concerns about some providers offering unproven and harmful treatments.” The new regulations require all providers of cell and tissue products operating outside hospitals to meet TGA quality and effectiveness requirements. Non-compliance may attract criminal charges.
  + May 2019 saw the release of the Australian Guidelines for the Prevention and Control of Infection in Healthcare*[[57]](#footnote-57)*.
  + [Public Health England](https://www.gov.uk/government/news/hajj-pilgrims-urged-to-be-aware-of-mers-cov-advice) has advised Islamic pilgrims from Britain participating in the Haj to avoid camels due to a potential risk of contracting Middle East Respiratory Syndrome coronavirus (MERS-CoV). It also warned against products such as raw camel milk and urged pilgrims to practice good hand hygiene. Dr Gavin Dabrera said. "Pilgrims returning from Hajj and Umrah with symptoms including fever and cough or shortness of breath, within 14 days of leaving the Middle East, should call their GP immediately or NHS 111 and mention their travel history".
  + In the UK, the National Institute for Health and Care Excellence (NICE), the advisor to England's National Health Service on costs and care quality, [recommended](http://www.pharmafile.com/news/522740/nice-recommends-msds-prevymis-cmv-prevention-following-allogeneic-haematopoietic-stem-ce) Merck's Prevymis (letermovir) for routine access for the prevention of cytomegalovirus (CMV) reactivation and disease in patients who have undergone an allogeneic hematopoietic stem cell transplant. This is reported to have followed an increase by Merck in a confidential discount offered. The European Commission approved the antiviral in January 2018.
  + The European Union and the US have fully implemented a mutual recognition agreement for inspections of manufacturing on bio- pharmaceutical sites for certain human medicines in their respective territories. The agreement was implemented after the recognition by the FDA of Slovakia as a partner in the agreement. European Union and American regulators will now rely on each other’s inspections for human medicines in their own territories, freeing up inspection teams to inspect facilities in other countries. The implementation of the mutual recognition agreement will continue with a view to expanding the operational scope to veterinary medicines, human vaccines and plasma-derived medicinal products.

# Research not included elsewhere

*A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.*

* + Scientists at the Versiti Blood Research Institute in Milwaukee are studying Von Willebrand disease, a common but often undiagnosed blood disorder, with the goals of improving diagnosis and treatment. Senior Investigator Robert Montgomery says adult women are affected most by symptoms. They can suffer severe postpartum haemorrhage and undergo unnecessary hysterectomies due to excessive menstrual bleeding that may have been related to von Willebrand disease.
    1. Versiti has been awarded $US13.2 million from the US National Institutes of Health, funding the next five years of its studies on VWD. Versiti will be working with partners, including research institutions, clinical care providers and other health systems.
    2. Researchers will be tracking bleeding over time in patients, comparing that with variables such as age and stress, as well as surgical history and genetics.
    3. In previous funding cycles, researchers found many people with the common form of the disease did not have a mutation in a gene that’s been linked to VWD; and that one of the tests commonly used to measure von Willebrand clotting factor was misidentifying the disease in African Americans, two-thirds of whom have differences in their genes that affect diagnosis of VWD.
  + A recent paper[[58]](#footnote-58) has looked at the effects of storage on blood plasma, from the viewpoint of its suitability for research. The scientists used gas and liquid chromatography to analyse samples that had been kept for up to 156 years in -80C storage. The team found that most metabolites were stable for up to seven years when stored at -80C and they recommend frozen samples be used soon after sampling[[59]](#footnote-59).
  + **Researchers from the University of Tokyo, Japan’s Rikin Institute and Stanford University say they have found an inexpensive and effective way to grow large numbers of haematopoietic stem cells (HSCs), or blood stem cells, in the lab. The cells were expanded and then successfully engrafted into mice[[60]](#footnote-60).**
  + Researchers have reported[[61]](#footnote-61) on the development of molecular tools to aid accurate diagnosis of inherited blood disorders, along with recent improvements in this field.

# Infectious diseases

*The NBA takes an interest in infectious diseases because: the presence of disease in individual donors (e.g. influenza), or potential disease resulting from travel (e.g. malaria) means a donor must be deferred; temporary disease burden within a community (e.g. dengue in North Queensland) may limit blood collection in the community for a time; and some people may not be permitted to donate at all (e.g. people who lived in the UK for a period critical in the history of vCJD). Blood donations are tested for a number of diseases (e.g. HIV and Hepatitis B), but there are also emerging infectious diseases for which it may become necessary to test in the future (e.g. Chagas disease, Zika virus and the tick-borne babesiosis and Lyme disease).*

## Mosquito-borne diseases

* + On 2 July, the World Health Organization (WHO) [issued an update on the Zika virus](https://www.who.int/emergencies/diseases/zika/epidemiology-update/en/) acknowledging that "Zika transmission persists but has generally been at low levels throughout 2018 to the present." Assessing risk, WHO said: "As of July 2019, a total of 87 countries and territories have had evidence of autochthonous mosquito-borne transmission of Zika virus (ZIKV), distributed across four of the six WHO Regions. Globally, 61 countries and territories in six WHO regions have evidence of established competent *Aedes aegypti* vectors but have not yet documented ZIKV transmission. Therefore, there is still a potential risk for ZIKV to spread to additional countries." WHO also [updated its advice to travellers](https://www.who.int/csr/disease/zika/information-for-travelers/en/), recommending that pregnant women avoid traveling to areas with Zika virus transmission, especially during outbreaks, based on the increased risk of severe birth defects during pregnancy. More generally: "all travellers should take appropriate measures to reduce the possibility of exposure to mosquito bites during the day and early evening hours and avoid risk of sexual transmission of Zika virus."
  + Ontera received a $US 982,593 contract from the US government's Intelligence Advanced Research Projects Activity (IARPA)[[62]](#footnote-62) to develop a point-of-care molecular test for Zika.
  + The Philippines declared a National Dengue Alert due to the increasing number of cases. The Department of Health reported 5,744 dengue cases in one week alone.
  + New research[[63]](#footnote-63) suggests that malaria could spread in somewhat cooler climates than might be expected, and this would reinforce the effect of climate change in extending the geographic areas where malaria is endemic.
  + Scientists at Duke University have been researching how human liver genes affect malaria’s growth, suggesting new ways to stop malaria before it spreads to the bloodstream[[64]](#footnote-64).
  + According to results from a systematic review and meta-analysis[[65]](#footnote-65), as many as 1 in 10 healthy blood donors globally may carry malaria parasites, making transfusion-transmitted malaria one of the most common transfusion- associated infections. Malaria parasitemia was particularly common in sub-Saharan Africa, with almost one-third of blood donors in Nigeria testing positive by microscopy.

## Influenza

* + WHO reported on 22 July that in Australia, H3N2 has been the dominant strain in the flu season, as it has been in the rest of Oceania and in South Africa. In temperate South America the dominant strain has been 2009 H1N1. From 24 June to 7 July, testing by WHO-affiliated laboratories round the world found that that 67.7 per cent of specimens were influenza A with the rest influenza B. Of subtyped influenza A strains, 62.7 per cent were H3N2 and the rest were 2009 H1N1. Of the characterized influenza B strains, 95.6 per cent were from the Victoria lineage and the remainder belonged to the Yamagata lineage.
  + In October 2018 the FDA approved Roche’s Xofluza for use in people aged 12 years of age and older with uncomplicated flu. Now a Phase III trial has shown **Xofluza is** well tolerated in children with flu. Xofluza was discovered by Shionogi. Roche holds worldwide rights to Xofluza excluding Japan and Taiwan, which will be retained exclusively by Shionogi.

## Ebola virus disease

* + On 4 July, WHO said the case count in the Democratic Republic of Congo since last August was 2,275 confirmed cases, with 1504 deaths. A fortnight later it declared the Ebola outbreak in the Congo an [international emergency](https://apnews.com/204fc739fc5846cdba4093ee65c4f7db).
  + Neighbouring South Sudan has a health system weakened by five years of civil war and is regarded as particularly vulnerable.
  + The doctor leading a Scots team working in Uganda to try to prevent the spread of Ebola has said the virus could easily spread round the world: “It only takes someone to get on a plane”.
  + The Democratic Republic of Congo’s health minister resigned. He had opposed the use of a back-up vaccine from Johnson & Johnson, which could then be introduced.

## MERS-CoV

* + WHO said on 22 July that the number of confirmed cases of MERS since April 2012 had been 2,449, of which 845 at least had been fatal.

## Other diseases

* + A randomized trial[[66]](#footnote-66) [[67]](#endnote-1)found that patients who underwent autologous haematopoietic stem cell transplantation (HSCT) and received GSK’s recombinant *herpes zoster* vaccine (Shingrix) had a lower incidence of the illness compared with HSCT patients receiving placebo. Those who received the vaccine also had reduced incidence of *herpes zoster* complications and duration of *herpes zoster*-associated pain.
  + The US Centers for Disease Control and Prevention (CDC) said on 22 July the number of measles cases recorded so far in 2019 was 1,148 across 30 states with the largest concentration being 623 in Brooklyn. Europe had reported 34,300 measles cases between 1 January and 7 May.
  + With the Hajj, or annual pilgrimage to Mecca, occurring from 9-14 August, 2 million pilgrims from over 183 countries were expected in Saudi Arabia, and the Ministry of Health in the Kingdom, along with officials in source countries, were recommending/ requiring all travellers be up to date with vaccinations, including measles-mumps-rubella; yellow fever if coming from or through areas at risk; meningococcal meningitis; poliomyelitis and seasonal influenza.

1. Amit X Garg et al., [*Safety of a Restrictive versus Liberal Approach to Red Blood Cell Transfusion on the Outcome of AKI in Patients Undergoing Cardiac Surgery: A Randomized Clinical Trial*](https://jasn.asnjournals.org/content/30/7/1294?utm_source=miragenews&utm_medium=miragenews&utm_campaign=news), published in the *Journal of the American Society of Nephrology*. JASN July 2019, 30 (7) 1294-1304; DOI: <https://doi.org/10.1681/ASN.2019010004> [↑](#footnote-ref-1)
2. Sydney A Jones et al., **“**Sepsis Attributed to Bacterial Contamination of Platelets Associated with a Potential Common Source — Multiple States, 2018”,[*MMWR Morb Mortal Wkly Rep*](https://www.cdc.gov/mmwr/volumes/68/wr/mm6823a2.htm?s_cid=mm6823a2_w%3Chttps://www.cdc.gov/mmwr/volumes/68/wr/mm6823a2.htm?s_cid=mm6823a2_w%3E)2019;68[23]:519-523). [↑](#footnote-ref-2)
3. Elshaday S Belay et al, Perioperative SSRI use is associated with an increased risk for transfusion in total hip and knee arthroplasty, [*The Journal of Arthroplasty*](https://www.sciencedirect.com/science/journal/08835403)*,* online 22June 2019, <https://doi.org/10.1016/j.arth.2019.04.057> [↑](#footnote-ref-3)
4. They examined 4,485 THA and 5,584 TKA cases from January 2013 to December 2017 [↑](#footnote-ref-4)
5. Naoki Notani et al., Fibrinogen level on admission is a predictive marker of the need for massive blood transfusion after pelvic fracture, *The American Journal of Emergency Medicine*, online 25 June 2019 <https://doi.org/10.1016/j.ajem.2019.06.043> [↑](#footnote-ref-5)
6. Massive transfusion was defined as “the transfusion of packed red blood cells (PRBCs) ≧10 units caused by bleeding within 24 h after admission.” [↑](#footnote-ref-6)
7. # Ryden J et al., “A longer duration of red blood cell storage is associated with a lower hemoglobin increase after blood transfusion: a cohort study”, [Transfusion.  2019; 59(6):1945-1952](https://reference.medscape.com/viewpublication/9553) (ISSN: 1537-2995)

   [↑](#footnote-ref-7)
8. # Ning S et al., “The association between platelet transfusions and mortality in patients with critical illness”, [Transfusion.  2019; 59(6):1962-1970](https://reference.medscape.com/viewpublication/9553) (ISSN: 1537-2995)

   [↑](#footnote-ref-8)
9. Elissa K Butler et al., “Association of blood component ratios with 24-hour mortality in injured children receiving massive transfusion” *Critical Care Medicine,*    47(7):975-983 · July 2019 Article DOI: [10.1097/CCM.0000000000003708](http://dx.doi.org/10.1097/CCM.0000000000003708) [↑](#footnote-ref-9)
10. Adam Irving et al., “Fresh red cells for transfusion in critically ill adults: An economic evaluation of the Standard Issue Transfusion Versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) clinical trial”, *Critical Care Medicine,*47(7):1 · April 2019 DOI: [10.1097/CCM.0000000000003781](http://dx.doi.org/10.1097/CCM.0000000000003781) [↑](#footnote-ref-10)
11. # Elizabeth St Lezin et al., “Therapeutic impact of red blood cell transfusion on anemic outpatients: the RETRO study”, [*Transfusion*](https://www.researchgate.net/journal/0041-1132_Transfusion)59(6) · March 2019  DOI: [10.1111/trf.15249](http://dx.doi.org/10.1111/trf.15249)

    [↑](#footnote-ref-11)
12. Sean D Pokorney et al., “[Association Between Warfarin Control Metrics and Atrial Fibrillation Outcomes in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation](https://jamanetwork.com/journals/jamacardiology/fullarticle/2737411),” published online 3 July 2019 JAMA Cardiology. doi:10.1001/jamacardio.2019.1960 [↑](#footnote-ref-12)
13. Colin W O’Brien at al., “Prevalence of Aspirin Use for Primary Prevention of Cardiovascular Disease in the United States: Results From the 2017 National Health Interview Survey”, [Annals of Internal Medicine,](https://annals.org/aim/article-abstract/2738925/prevalence-aspirin-use-primary-prevention-cardiovascular-disease-united-states-results) 23 July 2019. **DOI:** 10.7326/M19-0953 [↑](#footnote-ref-13)
14. The [FDA warns](https://www.fda.gov/drugs/bioterrorism-and-drug-preparedness/daily-aspirin-therapy) that aspirin’s side effects may include stomach or brain bleeding, kidney failure and certain kinds of stroke. [↑](#footnote-ref-14)
15. This was a single-arm, multicentre, open-label, Phase IIIb clinical trial evaluating the safety and tolerability of Hemlibra prophylaxis in people with haemophilia A with factor VIII inhibitors. There were 88 participants who had completed 24 weeks on study or discontinued, receiving subcutaneous Hemlibra 3 mg/kg/week for four weeks, followed by 1.5 mg/kg/week for the remainder of the treatment period. [↑](#footnote-ref-15)
16. The pooled data from the HAVEN studies demonstrated that a high proportion of patients experienced zero treated bleeds on Hemlibra, this being maintained over a median of 83 weeks. More than 87 per cent of patients had no treated joint bleeds and over 92 per cent of patients had no spontaneous bleeds in each interval from week 25. [↑](#footnote-ref-16)
17. [Therapeutic Levels of FVIII Generated by CRISPR/Cas9-mediated *in vivo* Genome Editing in Hemophilia A Mice](https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.professionalabstracts.com%2Fisth2019%2Fiplanner%2F%23%2Fpresentation%2F348&esheet=52009603&newsitemid=20190708005187&lan=en-US&anchor=Therapeutic+Levels+of+FVIII+Generated+by+CRISPR%2FCas9-mediated+in+vivo+Genome+Editing+in+Hemophilia+A+Mice&index=2&md5=b89ab4ad9a0bbbb8cab80e98371a4ca6) Haemophilic mice were initially treated with an adeno-associated virus (AAV) carrying a human FVIII coding sequence. The second stage was to inject lipid nanoparticles delivering a CRISPR/Cas9 nuclease designed to insert the FVIII coding sequence behind a strong natural liver cell promoter (LNP). The mice given both the AAV and the lipid nanoparticles were able to express normal human FVIII levels, and repeat dosing of the nanoparticles after a single dose of AAV was able to incrementally increase FVIII expression. The abstract and presentation are available for download at [https://casebia.com/news/](https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fcasebia.com%2Fnews%2F&esheet=52009603&newsitemid=20190708005187&lan=en-US&anchor=https%3A%2F%2Fcasebia.com%2Fnews%2F&index=3&md5=4108bf8526ae1bc32ae2356b9c8b21d8). [↑](#footnote-ref-17)
18. of the paradigm5 and paradigm6 trials [↑](#footnote-ref-18)
19. Barnes C, Chan A, Alamelu J, et al. *First report of an extended half-life FIX in previously untreated patients with haemophilia B,* and Carcao M, Kearney S, Taki M, et al. *Long-term safety and efficacy of nonacog beta pegol in previously treated children with haemophilia B, treated for at least 5 years.* Both were oral presentations at the 27th congress of the International Society on Thrombosis and Haemostasis (ISTH), Melbourne, 8 July 2019. [↑](#footnote-ref-19)
20. *People with Haemophilia and Female Carriers in Sweden have a Higher Risk of Developing Anxiety, Depression and Pain Based on Treatment Patterns as Compared to Matched Controls: Data from a Registry Study over a Period of 11 Years:* Oral Presentation # OC 32.3. 8 July 2019 [↑](#footnote-ref-20)
21. The company said some data added “to the growing body of evidence demonstrating the safety and efficacy of AFSTYLA [Antihemophilic Factor (Recombinant), Single Chain]. AFSTYLA (also known as rVIII-SingleChain), CSL Behring's recombinant factor VIII single-chain therapy for haemophilia A”. This is currently approved in over 40 countries including Australia, Japan, the European Union, the US, and Switzerland. Other sessions highlighted “new IDELVION [Coagulation Factor IX (Recombinant), Albumin Fusion Protein] data. IDELVION (also known as rIX-FP), is CSL Behring's long-acting recombinant factor IX albumin fusion protein for haemophilia B”. It is approved in over 40 countries including Australia, Japan, the European Union, the US and Switzerland. [↑](#footnote-ref-21)
22. *Factor VIII (FVIII)-Haplotype Mismatch Increases Risk of Inhibitor Development in the Treatment of Hemophilia A* (Tom Howard) [↑](#footnote-ref-22)
23. *Determining the Specificity of Commercially Available Thrombin Substrates* (S. Praporski); *Mechanisms for the Clearance and Recycling of Recombinant VWF D'D3 Albumin Fusion Protein* (Kim Lieu);  *Efficacy and safety of rIX-FP in surgery: an update from a phase 3b extension study* (Claude Négrier); *Population Pharmacokinetics of rVIII-SingleChain in Obese Previously Treated Patients with Severe Hemophilia A in Study CSL627\_1001; Higher trough levels, improved quality of life and reduced costs when switching to rIX-FP in a severe hemophilia B patient with considerable neurological disability* (Rosario Maggiore); *Systematic review of efficacy and factor consumption of long-acting recombinant factor VIII products for prophylactic treatment of hemophilia A* (Songkai Yan); *Treatment Success of rVIII-SingleChain in Obese Previously Treated Patients with Severe Hemophilia A in study CSL627\_1001* (Johnny Mahlangu); *Long-term efficacy and safety of recombinant factor IX fusion protein (rIX-FP) in previously treated patients with hemophilia B: Results from a phase 3b extension study* (Maria Elisa Mancuso); and *The Role of HLA-class-II (HLAcII) Molecules in Determining the Immunogenicity Potential of Therapeutic Factor VIII Proteins (tFVIIIs) in Hemophilia A (HA): The Gate Keeper Hypothesis (Vincent Diego)* [↑](#footnote-ref-23)
24. Andrew Cuthbertson, Chief Scientific Officer and Research and Development Director, said of the latter group: "Real world evidence can provide deep new insights that complement data acquired in clinical trials and can unlock the promise of novel bleeding disorder treatments. These presentations demonstrate our commitment to improving treatments and will provide valuable understanding to patients and physicians when creating a care plan."

    *Real-world use of recombinant factor IX albumin fusion protein (rIX-FP) in patients with hemophilia B: A multinational prospective, non-interventional, post-marketing surveillance study* (Johannes Oldenburg); *Comparison of FVIII prophylaxis treatment regimen and associated clinical outcomes between rVIII-SingleChain and other rFVIII products commonly used in German Hemophilia A patients* (Songkai Yan);  *Real-world utilization and bleed rates in patients with hemophilia B who switched to recombinant factor IX fusion protein (rIX-FP) in Italy, Belgium and the United……* (Patrick Sommerer); *Real-World Consumption rVIII-SingleChain: US Population Experience* (Michael Wang); *Prophylactic Factor VIII use and clinical outcomes in German Hemophilia A patients who switched to extended dosing intervals with long-acting rVIII-SingleChain* (Songkai Yan); and *Analysis of recombinant FVIII consumption and treatment outcomes and comparison with other FVIII products based on US Hemophilia A prophylaxis patient charts* (Songkai Yan) [↑](#footnote-ref-24)
25. *Taking a Flexible Approach in Hemophilia B* and *Improving Outcomes in Hemophilia A* [↑](#footnote-ref-25)
26. Pfizer and Sangamo Therapeutics are also partnered on an earlier-stage gene editing treatment for haemophilia B.  [↑](#footnote-ref-26)
27. Data from just two haemophilia A patients led to a significant price rise for Sangamo’s shares in April. The phase I/II [Alta trial](https://clinicaltrials.gov/ct2/show/NCT03061201) had by July enrolled ten patients, four of whom had received the highest dose which produced the most encouraging results. [↑](#footnote-ref-27)
28. The SB-525 ISTH presentation slides, which include the full data set, are available on Sangamo’s website in the Investors and Media section under [Events and Presentations](https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Finvestor.sangamo.com%2Fevents-and-presentations&esheet=52009519&newsitemid=20190705005294&lan=en-US&anchor=Events+and+Presentations&index=1&md5=f03dd6ddd8acfa6faaa4dd8c34fa8340). [↑](#footnote-ref-28)
29. Intravenous administration of FVIII can be a burden to people with haemophilia A and their families. Sub cutaneous delivery can therefore improve adherence to prophylaxis. [↑](#footnote-ref-29)
30. EXTEN-A was an open-label, multicentre study which evaluated the safety, tolerability and pharmacokinetics of BIVV001 in both a 25 IU/kg dose and 65 IU/kg dose cohort of subjects aged 18-65 years with severe hemophilia A. BIVV001 was found to be generally well tolerated with no development of inhibitors. [↑](#footnote-ref-30)
31. Initially, the aim is to raise awareness and to provide clinicians and scientists with a better understanding of the fundamentals of gene therapy, the treatment approach, research and clinical trials, safety and efficacy outcomes, how to identify patients who could benefit, and how to analyze implications of this new treatment approach alongside other available and emerging treatments for haemophilia. [↑](#footnote-ref-31)
32. Anita Shah et al., “[Direct comparison of two extended-half-life recombinant FVIII products: a randomized, crossover pharmacokinetic study in patients with severe hemophilia A](https://link.springer.com/article/10.1007%2Fs00277-019-03747-2)” online 24 June 2019 [Annals of Hematology](https://link.springer.com/journal/277). <https://doi.org/10.1007/s00277-019-03747-2> [↑](#footnote-ref-32)
33. From Bioverativ, a Sanofi company [↑](#footnote-ref-33)
34. # Katharine Batt et al., “Matching-adjusted indirect comparisons of annualized bleeding rate and utilization of BAY 94-9027 versus three recombinant factor VIII agents for prophylaxis in patients with severe hemophilia A”, *Journal of Blood Medicine*, 20 June 2019. Volume 10 pp 147-169 **DOI** <https://doi.org/10.2147/JBM.S206806>

    [↑](#footnote-ref-34)
35. The likelihood of organ damage, which includes kidney or liver failure and cardiopulmonary disease, increases with age. [Blood transfusions](https://www.mayoclinic.org/tests-procedures/blood-transfusion/about/pac-20385168) deliver additional normal red blood cells and are commonly used to treat acute SCD complications; but extra red blood cells can cause iron toxicity and [alloimmunization](https://transfusion.com.au/adverse_transfusion_reactions/alloimmunisation), which may result in a dangerous drop in haemoglobin levels. Red cell exchange transfusions replace sickled red blood cells with healthy ones, reducing the concentration of sickle cells but not increasing blood viscosity. However, exchanges cost more, take longer, and require more donor blood. [↑](#footnote-ref-35)
36. 150 adults at high risk of complications will be enrolled at eight clinical sites – the University of Pittsburgh, plus the [University of Illinois at Chicago](http://www.uic.edu) (UIC), [Duke University](http://www.duke.edu), [Emory University](http://www.emory.edu), [University of California San Francisco Benioff Children’s Hospital](https://www.ucsfbenioffchildrens.org/), the [University of Alabama at Birmingham](http://www.uab.edu), [Imperial College London](http://www.imperial.ac.uk) and [Henri Mondor Hospital](http://chu-mondor.aphp.fr/) in Paris. [↑](#footnote-ref-36)
37. Amsterdam, 13-16 June 2019 [↑](#footnote-ref-37)
38. The Phase I clinical trial can be found at [NCT02998450](https://www.clinicaltrials.gov/ct2/show/NCT02998450?cond=IMR-687&rank=1) and the Phase II trial, which is still recruiting participants, at [NCT03401112](https://www.clinicaltrials.gov/ct2/show/NCT03401112). [↑](#footnote-ref-38)
39. [PNS](https://c212.net/c/link/?t=0&l=en&o=2503064-1&h=3902592794&u=https%3A%2F%2Fwww.pnsociety.com%2Fi4a%2Fpages%2Findex.cfm%3Fpageid%3D3334&a=(PNS))  [↑](#footnote-ref-39)
40. held 22-26 June, in Genoa, Italy. [↑](#footnote-ref-40)
41. CIDP is an autoimmune disorder that affects the peripheral nerves. It can eventually lead to significant activity limitations of activity. About 30 per cent of patients will progress to wheelchair dependence if not treated. [↑](#footnote-ref-41)
42. The discussion was chaired by David Cornblath, Professor of Neurology, Johns Hopkins School of Medicine. The lectures included *Impact of over and under diagnosing CIDP* (Jeffrey A. Allen, Assistant Professor of Neurology, Feinberg School of Medicine, Northwestern University); *Finding the right treatment regimen for CIDP* (Pieter Van Doorn, Professor of Neuromuscular Disorders, Erasmus MC, University Medical Centre, Rotterdam); and *Optimising CIPD Guidelines* (Peter Van den Bergh, Director of the Neuromuscular Reference Centre, Cliniques Universitaires St. Luc, Brussels). [↑](#footnote-ref-42)
43. The HELP (Hereditary Angioedema Long-term Prophylaxis) Study was a multicentre, randomised, double-blind, placebo-controlled parallel group trial that evaluated the efficacy and safety of subcutaneously administered Takhzyro vs. placebo over 26 weeks in 125 patients 12 years of age or older with hereditary angioedema (HAE). Complete results from the Phase III HELP Study were published in the *Journal of the American Medical Association (JAMA)* on 27 November 2018. (Banerji A, Riedl MA, Bernstein JA, et al; for the HELP Investigators. “Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial”. JAMA. 2018;320(20):2108 [*JAMA The Journal of the American Medical Association*](https://www.researchgate.net/journal/0098-7484_JAMA_The_Journal_of_the_American_Medical_Association)320(20):2108 · November 2018 DOI: 10.1001/jama.2018.16773 ) [↑](#footnote-ref-43)
44. Riedl, MA et al., *Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks: Findings from the HELP study*. Poster Presentation. European Academy of Allergy and Clinical Immunology. Lisbon, Portugal. June 2019. [↑](#footnote-ref-44)
45. Doptelet was already approved in the US to treat thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure. The drug is also approved in Europe for the same liver disease indication. [↑](#footnote-ref-45)
46. The FDA approved Ultomiris for adults with PNH on [December 21, 2018](https://nam04.safelinks.protection.outlook.com/?url=https%3A%2F%2Fcts.businesswire.com%2Fct%2FCT%3Fid%3Dsmartlink%26url%3Dhttps%253A%252F%252Fnews.alexion.com%252Fpress-release%252Fproduct-news%252Falexion-receives-early-fda-approval-ultomiris-ravulizumab-cwvz-adults-par%26esheet%3D52006145%26newsitemid%3D20190703005355%26lan%3Den-US%26anchor%3DDecember%2B21%252C%2B2018%26index%3D2%26md5%3D2179d6e9dbf81cd1e3e0a0fda941bcfd&data=02%7C01%7C%7Ce4db08cc10514a7cb34d08d703f3aceb%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636982217430253558&sdata=lwQDeE0kcYTfqhW91uQwlcI2LgJLSCI1L4dy6AeXhjE%3D&reserved=0). The Japanese Ministry Of Health, Labour And Welfare approved Ultomiris as a treatment for adults with PNH on [June 18, 2019](https://nam04.safelinks.protection.outlook.com/?url=https%3A%2F%2Fcts.businesswire.com%2Fct%2FCT%3Fid%3Dsmartlink%26url%3Dhttps%253A%252F%252Fnews.alexion.com%252Fpress-release%252Fproduct-news%252Fultomiris-ravulizumab-receives-marketing-authorization-japans-ministry-he%26esheet%3D52006145%26newsitemid%3D20190703005355%26lan%3Den-US%26anchor%3DJune%2B18%252C%2B2019%26index%3D3%26md5%3D3a1eda5b33d0f8ce4f5d2158c186d573&data=02%7C01%7C%7Ce4db08cc10514a7cb34d08d703f3aceb%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636982217430263562&sdata=ezmfsB%2FybQVG%2BjpcAOwcl%2BsGzs4DrjIIp%2FRXuab%2B97o%3D&reserved=0). [↑](#footnote-ref-46)
47. <https://aptevotherapeutics.gcs-web.com/news-releases/news-release-details/aptevo-therapeutics-launches-new-3000-iu-ixinity-assay-offering> [↑](#footnote-ref-47)
48. Chief of HPB Surgery and Liver Transplantation at University Medical Center Groningen, The Netherlands.  [↑](#footnote-ref-48)
49. Globally, this is said to be the first human study where donor livers considered unsuitable for transplantation were refurbished and tested in a perfusion machine, using Hemopure. Sixteen suboptimal donor livers that were initially rejected by all transplant centres in The Netherlands underwent machine perfusion at the University Medical Center in Groningen. Eleven of the sixteen donor livers were then transplanted, resulting in 100 per cent graft and patient survival rates. [↑](#footnote-ref-49)
50. <https://www.biopharmadive.com/news/zolgensma-set-a-new-drug-pricing-bar-insurers-show-some-signs-of-pushback/558101/> [↑](#footnote-ref-50)
51. <https://investors.biomarin.com/2019-05-28-BioMarin-Announces-that-Phase-3-Cohort-of-Valoctocogene-Roxaparvovec-Gene-Therapy-Study-in-Severe-Hemophilia-A-Met-Pre-Specified-Criteria-for-Regulatory-Submissions-in-the-U-S-and-Europe?rel=0>. [↑](#footnote-ref-51)
52. Wayne Fu et al., “Characteristics and Scope of Training of Clinicians Participating in the US Direct-to-Consumer Marketplace for Unproven Stem Cell Interventions”, [bit.ly/2XzKGjt](http://bit.ly/2XzKGjt) JAMA, online 25 June, 2019. *JAMA.* 2019;321(24):2463-2464. doi:10.1001/jama.2019.5837 [↑](#footnote-ref-52)
53. The exception, David Kessler, entered academia before accepting his current position as chair of the board of directors at the Center for Science in the Public Interest, a non-profit nutritional science advocacy group. [↑](#footnote-ref-53)
54. [According to a new report](https://www.cdc.gov/media/releases/2019/p0627-americans-hiv-test.html) [↑](#footnote-ref-54)
55. The Department of Health and Human Services has proposed [Ending the HIV Epidemic: A Plan for America](https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview) that aims to reduce new HIV infections by 75 per cent in five years and at least 90 per cent in 10 years. It would increase resources used for public health, technology and experts in areas with the highest risk for HIV. [↑](#footnote-ref-55)
56. Pharmaceutical Benefits Scheme [↑](#footnote-ref-56)
57. Australian Guidelines for the Prevention and Control of Infection in Healthcare, Canberra: National Health and Medical Research Council (2019). [www.nhmrc.gov.au](http://www.nhmrc.gov.au). [↑](#footnote-ref-57)
58. Antje Wagner-Golbs, “Effects of Long-Term Storage at −80 °C on the Human Plasma Metabolome”, Metabolites 2019, 9(5), 99; <https://doi.org/10.3390/metabo9050099> [↑](#footnote-ref-58)
59. Improving chromatography’s ability to detect small changes is discussed in the article, [Using Narrow Bore Columns to Enhance Sensitivity for LC-UV and LC-MS Analyses](https://ilmt.co/PL/QJoR) published 12 June 2019 in *Chromatography Today.* [↑](#footnote-ref-59)
60. Wilkinson, A.C. et al. “Long-term ex vivo haematopoietic-stem-cell expansion allows nonconditioned transplantation”. Published 29 May *Nature* 571, 117-121 <https://www.nature.com/articles/s41586-019-1244-x> [↑](#footnote-ref-60)
61. Bastida JM, Benito R, Lozano ML, et al. [Molecular diagnosis of inherited coagulation bleeding disorders](https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0039-1687889) [published online April 29, 2019]. Seminars in Thrombosis and Hemostasis. doi:10.1055/s-0039-1687889 [↑](#footnote-ref-61)
62. IARPA is modelled on DARPA, the Defense Advanced Research Projects Agency. IARPA is part of the Office of the Director of National Intelligence, which serves as the head of the US intelligence community. [↑](#footnote-ref-62)
63. Jessica L Waite et al., “Exploring the lower thermal limits for development of the human malaria parasite, *Plasmodium falciparum****”,*** *Biology Letters,* 26 June 2019, <https://doi.org/10.1098/rsbl.2019.0275> [↑](#footnote-ref-63)
64. Rene Raphemot et al., "Discovery of Druggable Host Factors Critical to Plasmodium Liver-Stage Infection” Cell Chemical Biology, 27 June 2019. <https://doi.org/10.1016/j.chembiol.2019.05.011> [↑](#footnote-ref-64)
65. Ehsan Ahmadpour et al., “Transfusion-Transmitted Malaria: A Systematic Review and Meta-analysis” Open Forum Infectious Diseases, Volume 6, Issue 7, July 2019, ofz283, <https://doi.org/10.1093/ofid/ofz283> [↑](#footnote-ref-65)
66. Adriana Bastidas et al., “Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial”. [*JAMA*](https://jamanetwork.com/journals/jama/fullarticle/2737683). 2019;322(2):123-133. doi:10.1001/jama.2019.9053 [↑](#footnote-ref-66)
67. [↑](#endnote-ref-1)