

BCG 101

THE JOURNEY OF BCG: 1906-2022

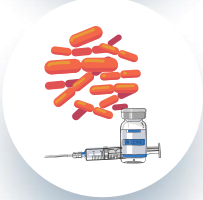
1906

Mycobacterium bovis
Albert Calmette and
Camille Guérin
started developing a
vaccine for TB prevention.
Pasteur Institute,
France



1921

**bacillus Calmette-Guérin
(BCG) vaccine**
BCG confirmed as a safe
vaccine for use in humans
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1972

**BCG for treatment of
non-muscle invasive
bladder cancer**
Alvaro Morales
Queen's
University,
Canada



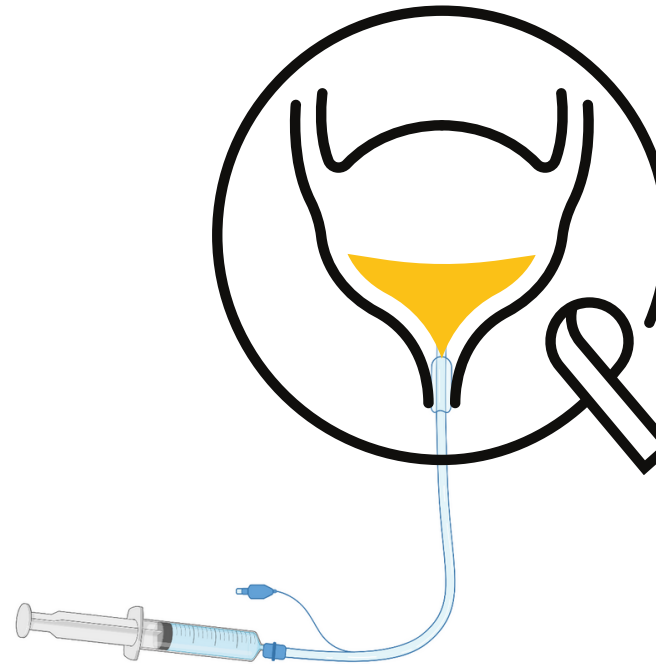
2012

BCG shortage
Closing down of Sanofi
Pasteur plant due to mold
contamination.



2021

**Approval of VERITY-BCG
from Serum Institute of
India.**



Madhuri Koti, DVM, MVSc, PhD



March 8, 2022



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Outline

Bladder cancer

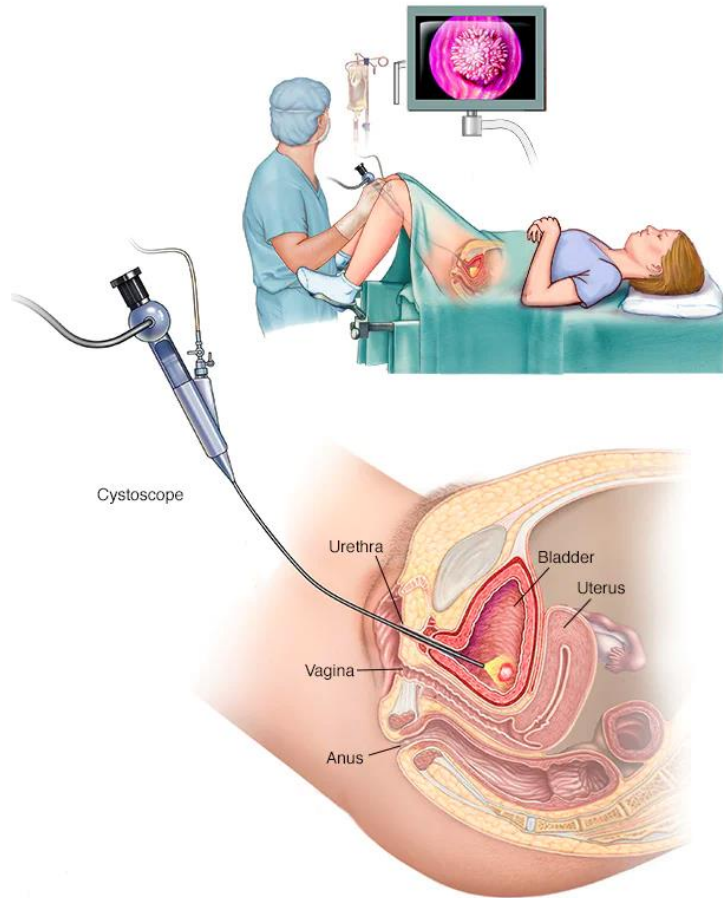
History of bacillus Calmette Guérin (BCG)

BCG immunotherapy for bladder cancer

BCG manufacturer (Merck, VERITY)

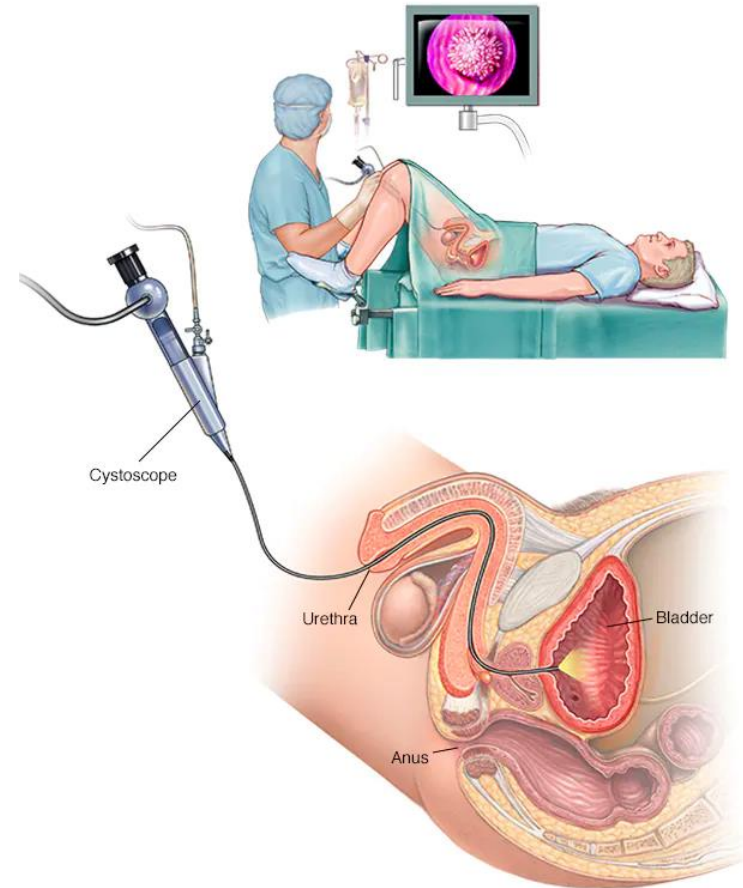
Q&A

Bladder cancer: diagnosis



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Female



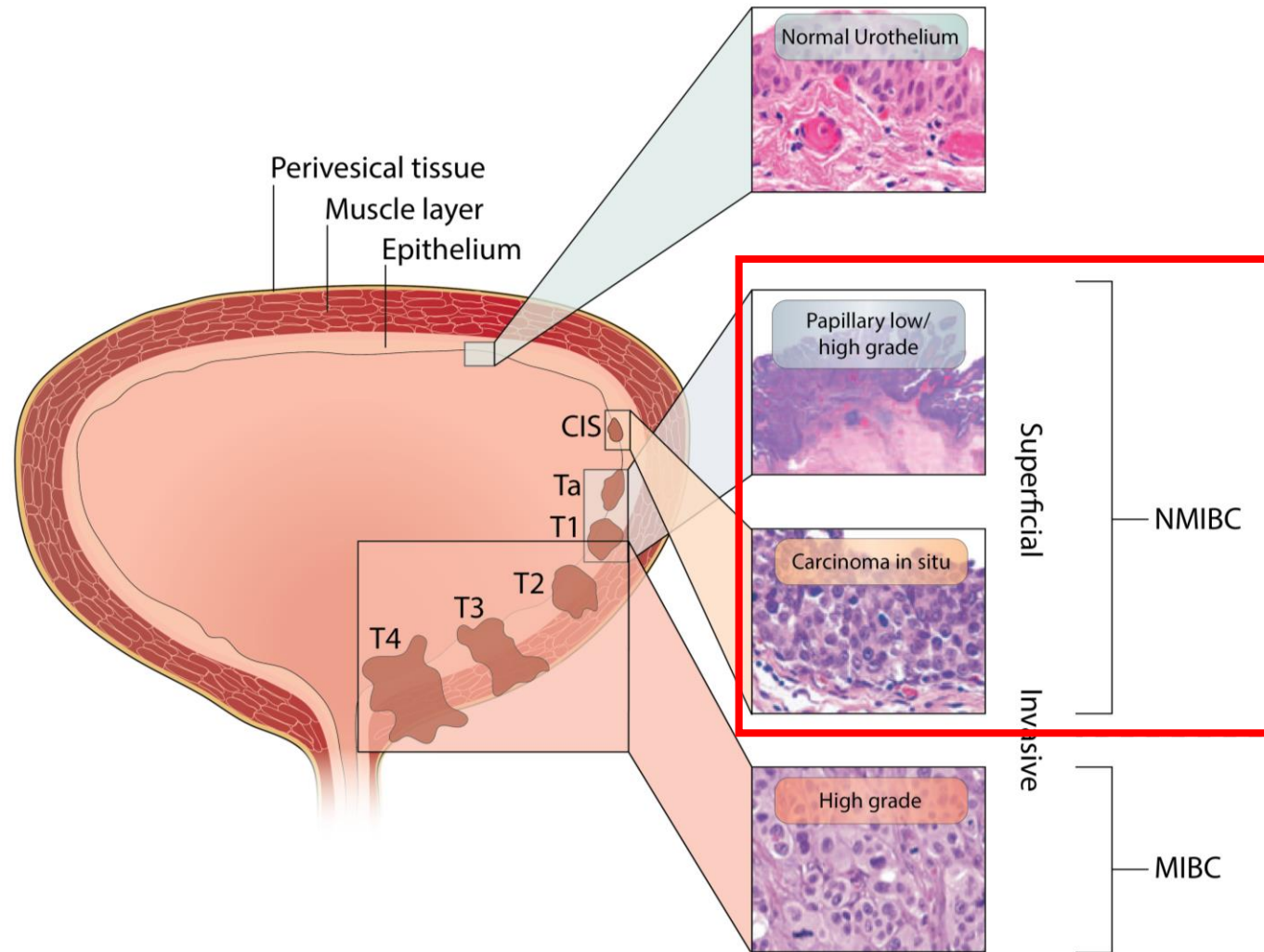
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Male

<https://www.mayoclinic.org/diseases-conditions/bladder-cancer/diagnosis-treatment/drc-20356109>



Bladder cancer: treatment



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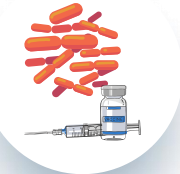
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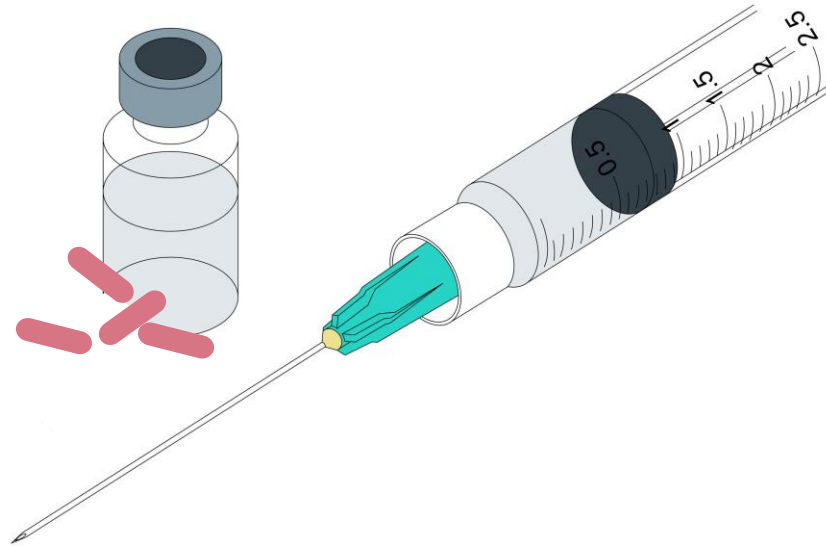
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What is BCG?



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History of BCG



Camille Guérin

1872–1961

Albert Calmette

1863–1933

<https://www.cnn.com/2013/05/22/health/gallery/discover-cure-lifeswork/index.html>

Distribution of BCG

July 1950

157

Freeze-Dried (Lyophilized) BCG

By F. VAN DEINSE, *Chief*, and FRANÇOISE SENECHAL, *Assistant*
BCG Dept., Institut Pasteur, Paris

Introduction

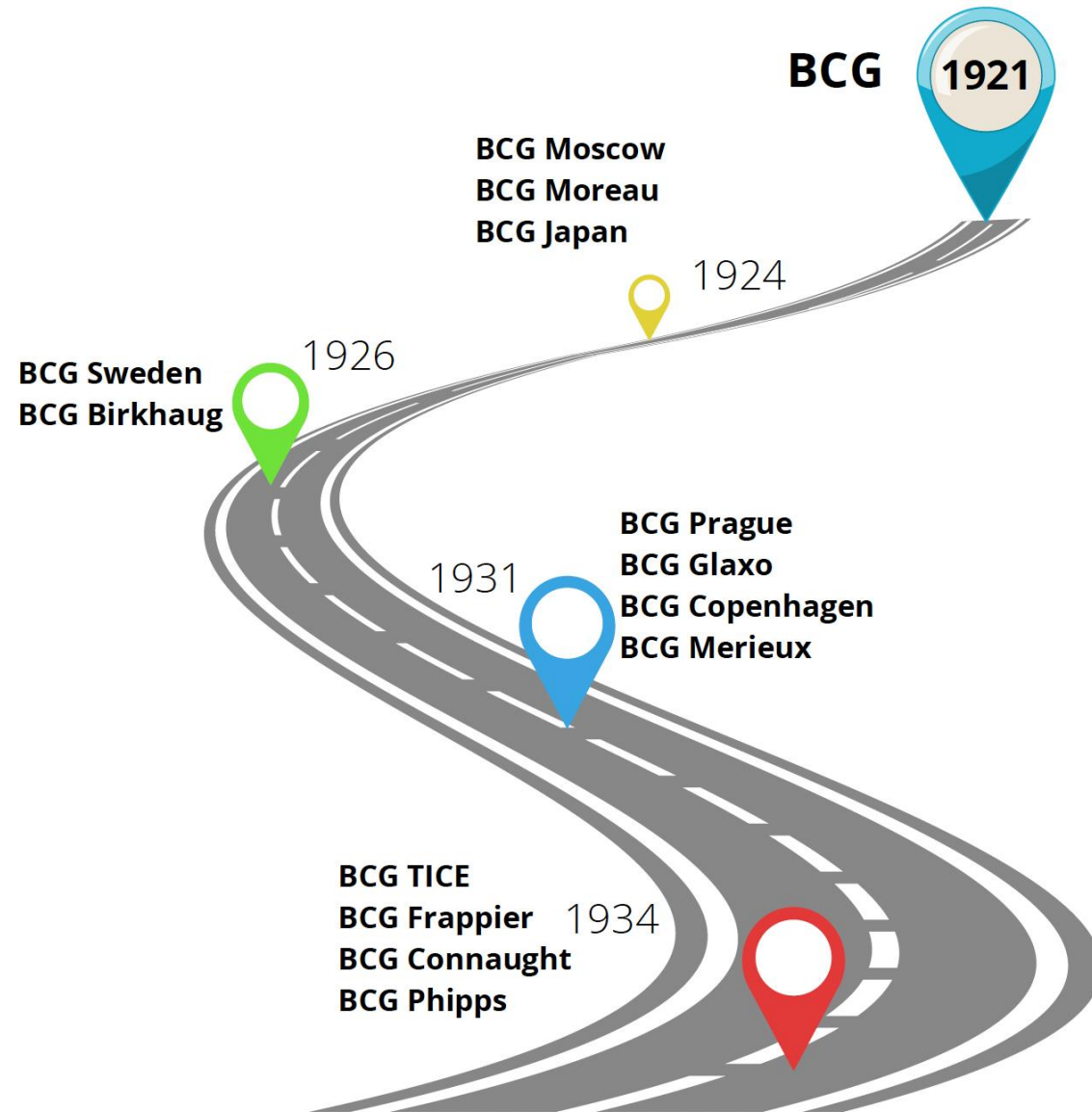
The only way at present of preserving BCG vaccine so as to allow transport for long distances and distribution in tropical countries is the freeze-drying technique.

Freezing in itself is an excellent procedure for the conservation of micro-organisms and biological substances. As early as 1898 Brown and Escombe stated that grains were still able to germinate after exposure to the temperature of liquid air (-183°C.) for 110 hours and in 1900 MacFadyen demonstrated the survival of micro-organisms at

desiccation on biological substances was the increasing concentration of the different salts contained in the suspension liquid in the course of drying, and that the problem was to find a means of transforming the material and drying it without its being exposed to the deleterious action of concentrating salts in the mixture. The solution of the problem has been found by drying after rapid freezing.

Shackell in 1909 was the first author who described the technique of freeze-drying for the conservation of micro-organisms, viruses, and other active biological substances.

What are BCG strains?



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BCG immunotherapy for non-muscle invasive bladder cancer

THE JOURNAL OF UROLOGY

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INTRACAVITARY BACILLUS CALMETTE-GUERIN IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS

A. MORALES,* D. EIDINGER AND A. W. BRUCE

From the Departments of Urology, and Microbiology and Immunology, Queen's University, Kingston, Ontario, Canada

ABSTRACT

Patients with recurrent, superficial bladder tumors have been treated by vesical and intradermal administration of Bacillus Calmette-Guerin. The pattern of recurrence in 9 patients has been altered favorably. Although the findings are still preliminary they appear to hold promise of a new therapeutic approach to the treatment of a group of neoplasms for which effective therapy is still lacking.

50 years of BCG in non-muscle invasive bladder cancer

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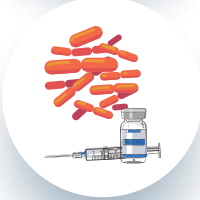
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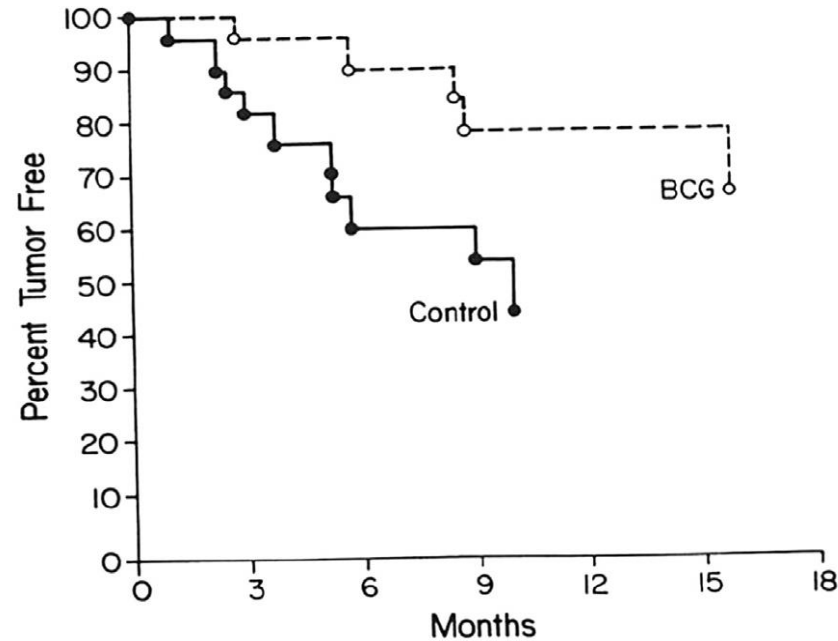
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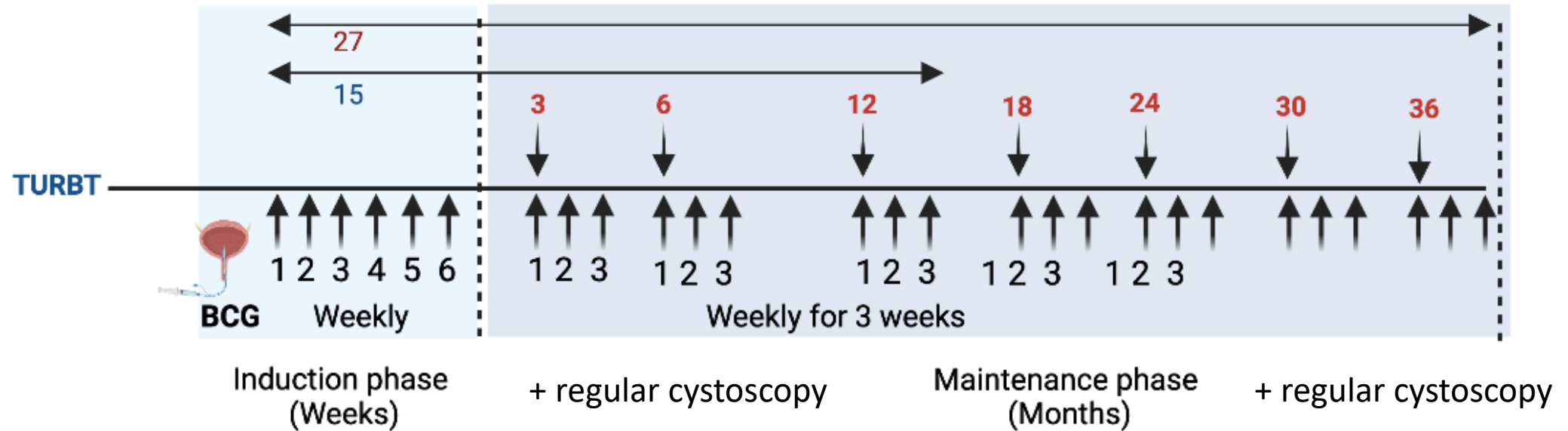
2021

Approval of VERITY-BCG from Serum Institute of India.



D.L. Lamm and A. Morales, *Vaccine*, 2021

BCG treatment schedule: NMIBC



Alvaro Morales



Donald Lamm



What is the mode of action of BCG?

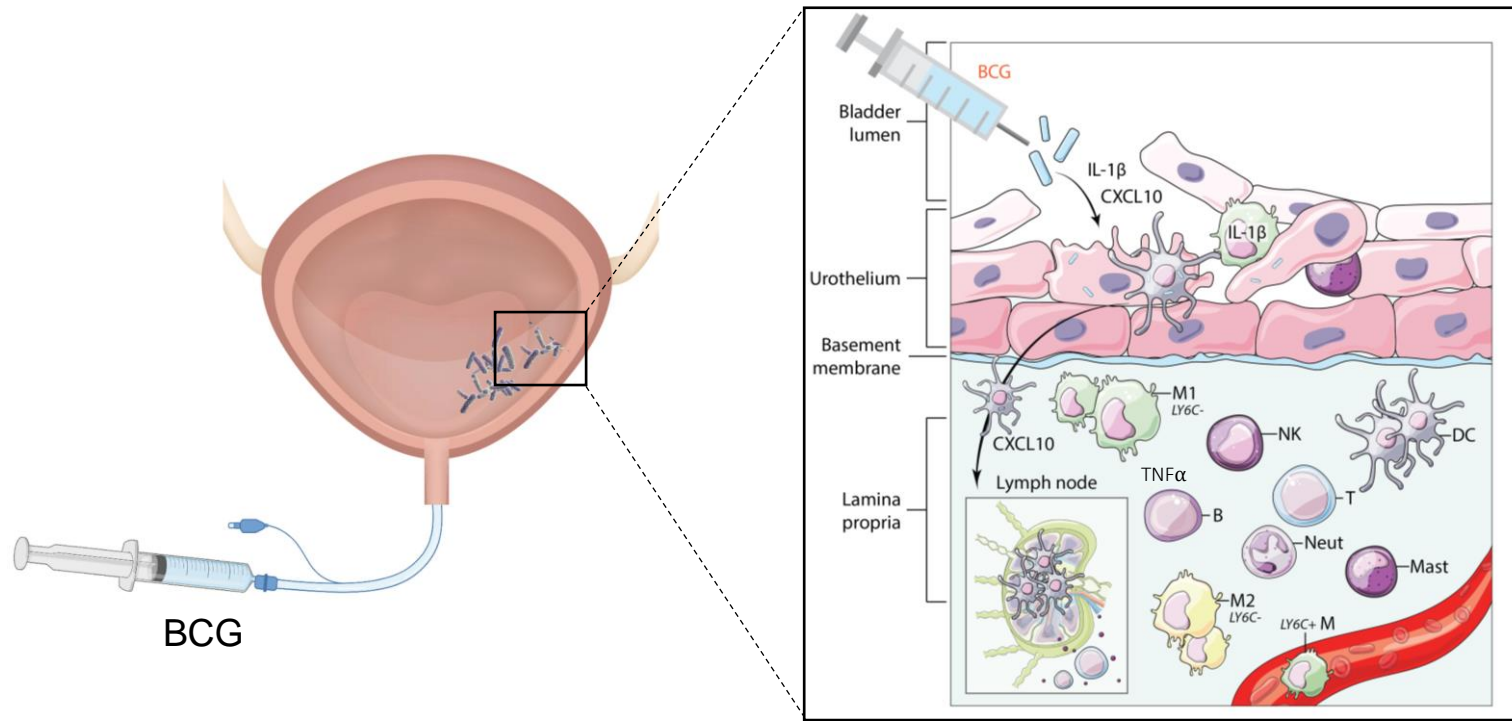
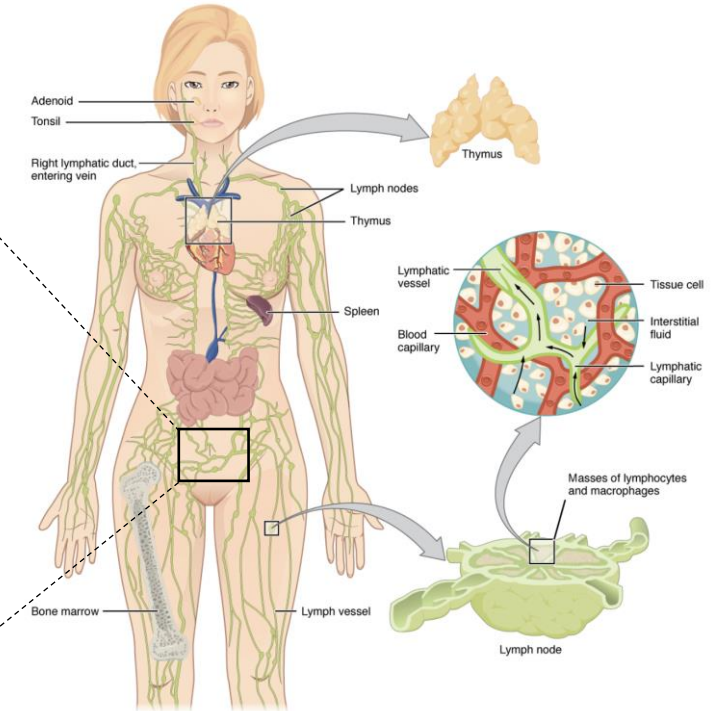


Image by Sarah Nersesian



<https://opentextbc.ca/anatomyandphysiologyopenstax/chapter/anatomy-of-the-lymphatic-and-immune-systems/>



BCG shortage

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No TB vaccine until 2013 says Canadian company



BCG vaccine used in Nunavut to protect newborns

CBC News · Posted: Jun 22, 2012 10:39 AM CT | Last Updated: June 22, 2012

The Canadian manufacturer of the BCG tuberculosis vaccine says it won't be making more until late 2013.

The vaccine is offered to newborns in Nunavut and helps protect against serious forms of the disease for two years. The rate of TB in Nunavut is about 75 times the national average, according to the Canadian Medical Association.



Sanofi Pasteur, the manufacturer of the BCG vaccine, estimates production will resume in late 2013 after renovations to its Ontario manufacturing facility are completed. (CBC)

<https://www.cbc.ca/news/canada/north/no-tb-vaccine-until-2013-says-canadian-company-1.1172454>

Commercial BCG preparations

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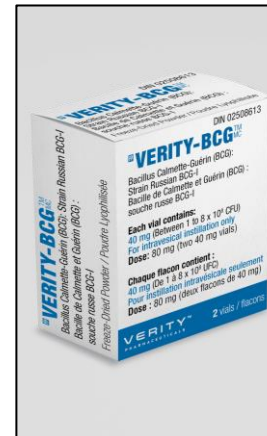
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The VERITY-BCG™ Solution

Verity-BCG™ from the Serum Institute of India (SIIPL; world's largest vaccine manufacturing facility)



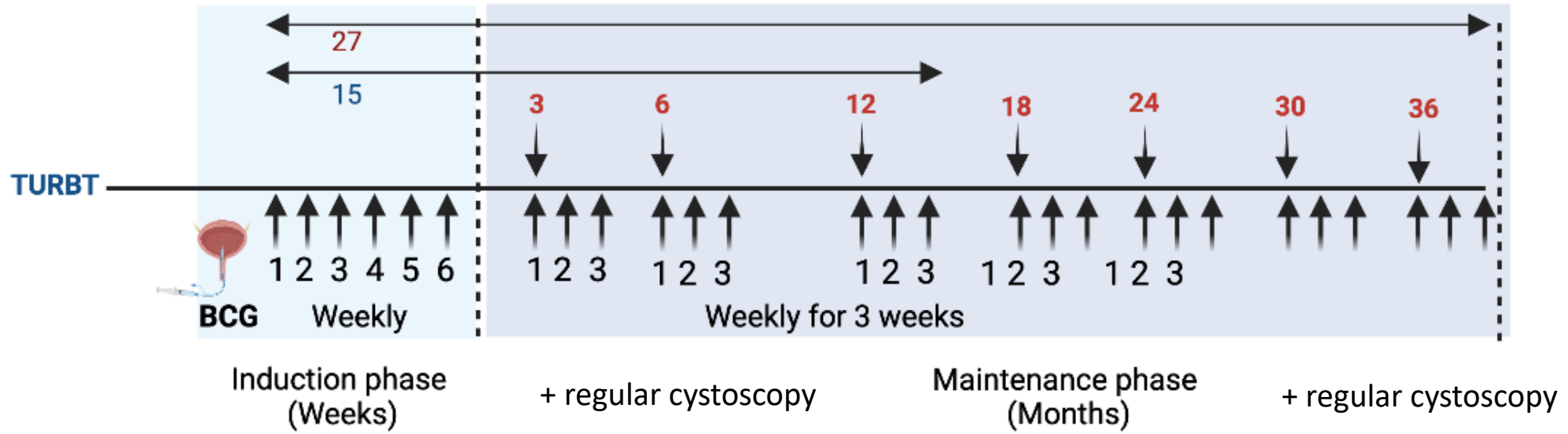
https://www.seruminstitute.com/about_us.php

- Adjuvant therapy after TURBT of a primary or relapsing superficial papillary urothelial cell carcinoma of the bladder stage Ta (grade 2 or 3) or T1 (grade 1, 2, or 3), without concomitant CIS.
- Stage Ta grade 1 papillary tumors, at a high risk (> 50%) of tumor recurrence.

Ref: 1) VERITY-BCG™ Canadian Product Monograph. https://veritypharma.com/wp-content/uploads/2021/02/VERIT-BCG-Product-Monograph_EN.pdf Accessed June 29, 2021



The VERITY-BCG™



- VERITY-BCG 80 mg – $1-16 \times 10^8$ CFUs
 - 80 mg of the lyophilized powder
- OncoTICE 50 mg – $1-8 \times 10^8$ CFUs
 - 50 mg wet weight
- ImmuCyst 81 mg - $10.5 \pm 8.7 \times 10^8$ CFUs
 - 81 mg dry weight



Is there a difference in response to BCG strain used for oncological preparations?

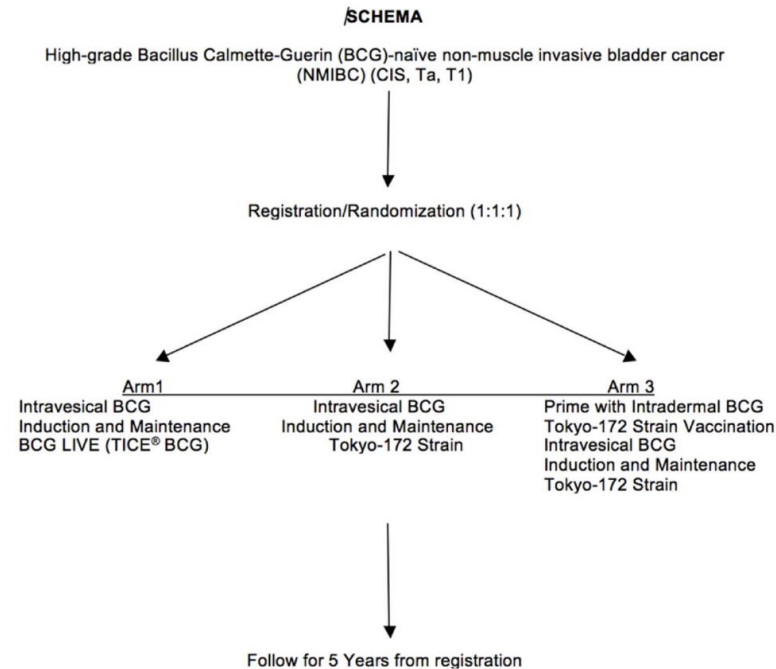


Figure 1. S1602 Study Schema

Svatek et al., 2019. *European Urology Focus*.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6581029/>

Comparative Effectiveness of Intravesical BCG-Tice and BCG-Moreau in Patients With Non-muscle-invasive Bladder Cancer

David D'Andrea,¹ Francesco Soria,^{1,2} Mohammad Abufaraj,^{1,3} Mario Pones,¹ Paolo Gontero,² André T. Machado,⁴ Ricardo Waksman,⁴ Dmitry V. Enikeev,⁵ Petr V. Glybochko,⁵ Sanarely Pires Adonias,⁴ William Carlos Nahas,⁴ Shahrokh F. Shariat,^{1,5,6,7} Daher C. Chade⁴



Article

Compared Efficacy of Adjuvant Intravesical BCG-TICE vs. BCG-RIVM for High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC): A Propensity Score Matched Analysis

Francesco Del Giudice^{1,2,*}, Rocco Simone Flammia¹, Benjamin I. Chung², Marco Moschini³, Benjamin Pradere⁴, Andrea Mari⁵, Francesco Soria⁶, Simone Albisinni⁷, Wojciech Krajewski⁸, Tomasz Szydelko⁸, Ekaterina Laukhtina^{4,9}, David D'Andrea⁴, Andrea Gallioi¹⁰, Laura S. Mertens¹¹, Martina Maggi¹⁰, Alessandro Sciarra¹⁰, Stefano Salciccia¹, Matteo Ferro¹², Carlo Maria Scornajenghi¹, Vincenzo Asero¹, Susanna Cattarino¹, Mario De Angelis³, Giovanni E. Cacciamani¹³, Riccardo Autorino¹⁴, Savio Domenico Pandolfo^{14,15}, Ugo Giovanni Falagarò¹⁵, Nicola D'Altilla¹⁶, Vito Mancini¹⁶, Marco Chirico¹⁶, Francesco Cinelli¹⁶, Carlo Bettocchi¹⁶, Luigi Cormio¹⁶, Giuseppe Carrieri¹⁶, Ettore De Berardinis^{1,†}, Gian Maria Busetto^{16,†} and on behalf of European Association of Urology (EAU)—Young Academic Urologists (YAU) Urothelial Cancer Working Party[†]

2022



The Canadian Bladder Cancer Research Network



Dr. Wassim Kassouf



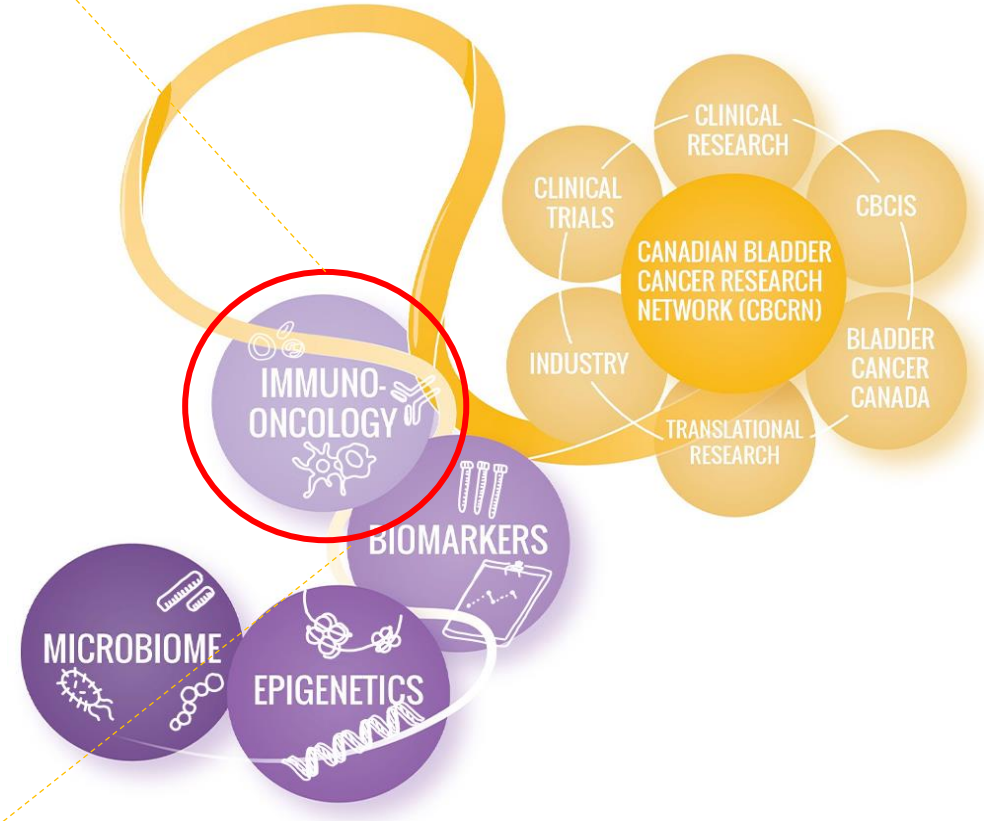
Dr. Peter Black



Dr. Robert Siemens



Dr. David Berman



Help BCG work better

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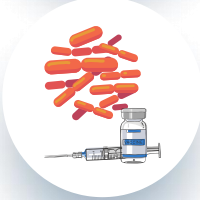
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- Quality of life; diet and exercise
- **Quit smoking!**
- Detailed history (gender, past infections, vaccination status, smoking)
- Participate in discussions on research needs questions and ...clinical trials!
- Advocate for research (and funding) in bladder cancer
- Help reduce financial toxicity.

Acknowledgements

- Dr. Alvaro Morales
- Dr. Donald Lamm
- Trainees
- Collaborators



- VERITY Pharmaceuticals
- Patients



THANK YOU



Dr. Alvaro Morales
Dept. of Urology



Petit Chabonne - 9-11-88
Santoni - Guérin
Petit Chabonne - Vauveuil
86210 Bormeuil - Matours

RECEIVED
NOV 24 1988
RECEIVED

Professeur Alvaro Morales
M.D., F.R.C.S (C)
Professeur and Chairman
Department of Urology

Professeur;
Le Professeur Steg m'a communiqué
votre lettre, j'ai tardé à répondre car je
devais faire une cystoscopie; elle a été faite ce
matin, et s'est révélée parfaite.

Par un saignement, j'ai su en
Août 1982 que j'avais des polypes.
Le Professeur Steg m'a opéré.

4 fois, la dernière intervention est de
février 1986.

À partir de Mars 1985 j'ai eu
24 instillations de B.C.G. qui ont été arrêtées
en novembre 1986 et depuis juillet 1986 on ne
trouve plus rien.

Voilà l'aventure de la fille du
Professeur Guérin, je suis heureuse de vous la
raconter, et, vous fait un grand infini de
vous en être inquiété.

Très respectueusement

Santoni - Guérin

Fig. 2. Letter written by Professor Guérin's daughter in 1988. The last two paragraphs read: "Starting in March 1985 I received 24 instillations of BCG which were stopped in November 1986 and since July 1986 nothing else has been found. There you have the story of the daughter of Professor Guérin. I am pleased to share it with you and I am grateful to you for having expressed your concerns."

D.L. Lamm and A. Morales, Vaccine, 2021

Selected resources

- <https://www.nature.com/articles/ni1105-1063>
- <https://www.sciencedirect.com/science/article/pii/S1473309921004035?via%3Dihub>
- [https://www.eu-openscience.europeanurology.com/article/S1569-9056\(06\)00142-4/fulltext](https://www.eu-openscience.europeanurology.com/article/S1569-9056(06)00142-4/fulltext)
- <https://www.sciencedirect.com/science/article/pii/S0264410X2101046X?via%3Dihub>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6581029/>
- <https://cuaj.ca/index.php/journal/article/view/7367/5010>
- <https://bcan.org/wp-content/uploads/2018/02/BCG-Expert-Explanation-2.pdf>